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NATURE AND QUANTITATIVE DETERMINATION OF THE REDUCING SUBSTANCE IN NORMAL AND PATHOLOGIC CEREBROSPINAL FLUID*

OSCAR M. SCHLOSS, M.D., AND LOUIS C. SCHROEDER, MD.
NEW YORK

I. INTRODUCTION

During the past year we have had opportunity to make a series of quantitative determinations of the reducing power of various specimens of normal and pathologic cerebrospinal fluid, and also to carry out certain observations concerning the nature of the reducing substance. The data thus derived serve as the basis of this communication.

II. THE NATURE OF THE REDUCING SUBSTANCE

It is generally assumed that the reducing agent in cerebrospinal fluid is dextrose — the sugar of blood and body fluids. A review of the literature, however, discloses that there has been considerable divergence of opinion. Halliburton,[1] whose views are quoted in several current textbooks, concluded that the reducing substance was pyrocatechin or a pyrocatechin derivative. Connall[2] states that it is galactose, although he gives no references or experimental data to uphold this view. The observations of Nawratski,[3] Zdarek,[4] Rossi[5] and others, however, indicate that the reducing agent is a fermentable, dextrorotatory sugar, presumably dextrose.

---

* From the Children's Wards and the Pathological Laboratory, Bellevue Hospital, New York.

* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May, 1915.

1. Halliburton: Text Book of Chemical Physiology and Pathology, London, 1891. Thompson, Hill and Halliburton: Observations on the Cerebrospinal Fluid in the Human Subject, Trans. Path. Soc., London, 1899, liv, 344.

2. Connall: A Study of the Cerebrospinal Fluid in the Infective Diseases of the Meninges with Special Reference to Cerebrospinal Fever, Quart. Jour. Med., 1909, iii, 152.

3. Nawratski: Zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chem., 1897, xxiii, 533.

4. Zdarek: Ein Beitrag zur Kenntniss der Cerebrospinalflüssigkeit, Ztschr. f. physiol. Chem., 1902, xxxv, 211.

5. Rossi: Sulla natura della sostanza reducente contenuta nel liquido cephalorachidea, Clin. med. ital., 1899, xxxviii, 422.

In order to obtain additional evidence on this subject we made the following experiments:

Mixed specimens of practically normal[6] cerebrospinal fluid, from 460 to 700 c.c. each, were precipitated with absolute alcohol, filtered and evaporated at a low temperature in slightly acid solution to a volume of 30 c.c. The resulting solution was filtered and subjected to tests, the results of which may be summarized as follows:[7]

1. Quantitative determination of the reducing substance as dextrose by Benedict's solution gave percentages of 0.86 to 1.3.

2. The solutions were dextrorotatory and the rotation corresponded to a percentage of dextrose nearly identical with that obtained by Benedict's reagent.[8]

3. The solutions were fermented by yeast with the production of alcohol and carbon dioxid. The mixture was acid in reaction (litmus).

4. A crystallin osazone was obtained which was insoluble in hot water, soluble in alcohol and pyridin and melted at 200 to 208 C.

5. A repetition of the procedure of Halliburton gave no precipitate of pyrocatechin.

It has been found by a number of observers that the reducing substance in cerebrospinal fluid is destroyed by bacterial growth in twenty-four to seventy-two hours. We were able to confirm this observation on a number of occasions. It therefore seemed only rational to assume that if the reducing action of cerebrospinal fluid were due to pyrocatechin, the reducing power of this substance should be destroyed by bacterial growth. With this idea in mind the following experiment was made:

Pyrocatechin was dissolved in nutrient broth in sufficient quantity to give a reducing action equal to normal cerebrospinal fluid. This reducing power was not appreciably decreased by bacterial growth.

The observations cited indicate that there is no basis for the belief that the reducing substance in normal cerebrospinal fluid is pyrocatechin. Moreover, our results indicate that this agent is a monosaccharid, probably dextrose.

III. QUANTITATIVE DETERMINATIONS OF THE REDUCING AGENT IN CEREBROSPINAL FLUID

But few determinations of the reducing agent in cerebrospinal fluid have been made and these concerned normal or nearly normal

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6. Part of the fluid in one specimen was from a patient affected with hydrocephalus, and from one with tuberculous meningitis, but both specimens of fluid contained a normal amount of the reducing substance.

7. These experiments were made on three separate collections of material.

8. The exact results were as follows:

Specimen	Dextrose P. C. Benedict's Solution	Dextrose P. C. Polarimeter
1	0.86	0.77
2	0.97	1.2
3	1.3	1.12

material. Owing to the small amount of this substance usually present, a number of the estimations were made on mixed specimens of fluid obtained from several patients and therefore give no idea of the normal fluctuations. So far as we can ascertain, there have been no quantitative determinations of the reducing power of cerebrospinal fluid in meningeal diseases.

TECHNIC

By means of the method of Lewis and Benedict[9] for the quantitative determination of blood sugar we were able to make accurate determinations of the reducing power of cerebrospinal fluid by using quantities of 5 c.c. or even less.[10] During the course of the work qualitative tests for comparison were made with Benedict's and Fehling's solutions. We found the reagent of Benedict the more satisfactory, and after experiment adopted the following procedure. To exactly 5 c.c. of the reagent were added 12 drops of cerebrospinal fluid. The mixture was kept at boiling temperature for one to two minutes and allowed to cool spontaneously. The test was usually positive when the fluid contained 0.05 per cent. or more of dextrose.

The Sugar Content of Normal Cerebrospinal Fluid.—The results for normal fluids were obtained from a study of material from forty-five infants and children (Table 1) on whom lumbar puncture was done as a diagnostic procedure. There were a number of cases of meningism, but all fluids showed a normal cell count and no increase of globulin (Kaplan, Noguchi). The maximum amount of sugar found in normal cerebrospinal fluid was 0.139 per cent., the minimum 0.054 per cent. As shown in the table, the amount of sugar contained in the different fluids varied greatly. The cause of this variation is not apparent, but it seems probable that the amount of sugar in each individual may vary from time to time, as is true of blood sugar. Owing to the method of obtaining cerebrospinal fluid, it is impossible to determine the possible influence of diet and other factors, which we know are capable of changing the sugar content of the blood. It is of great interest that the normal variation in the amount of sugar in cerebrospinal fluid is very close to that which obtains for blood. It therefore seemed of interest to ascertain whether there is any correspondence between the blood sugar and the cerebrospinal fluid sugar in the individual case. Accordingly, in ten cases we have made sugar determinations on blood and cerebrospinal fluid which

9. Lewis and Benedict: A Method for the Estimation of Sugar in Small Quantities of Blood, Jour. Biol. Chem., 1915, xx, 61.

10. Five cubic centimeters of cerebrospinal fluid was delivered into a 25 c.c. volumetric flask from an Ostwald-Folin pipet; 10 c.c. of a saturated aqueous solution of picric acid were added; the mixture made up to 25 c.c. with water and filtered. Aliquots of 8 c.c. were used and to each was added 2 c.c. of the aqueous picric solution. Otherwise the method corresponds to the description of Lewis and Benedict.

TABLE 1.—THE PERCENTAGE OF DEXTROSE IN NORMAL CEREBROSPINAL FLUID

No.	Diagnosis	General Characteristics	Per Cent. Dextrose
1	Lobar pneumonia, otitis media	Clear; no increase of pressure; no globulin; no cells	0.0756
2	Acute tonsillitis, meningism	Clear; no cells; no globulin; pressure moderately increased	0.09
3	Congenital deformity, lobar pneumonia	Normal	0.1390
4	Tuberculosis of spinal column	Normal	0.08
5	.....	Normal	0.065
6	Convulsions	Normal	0.08
7	.....	Normal	0.0992
8	Tuberculous bronchopneumonia, otitis media, rickets	Normal	0.0692
9	.....	Normal	0.0674
10	Bronchopneumonia	Normal	0.0348 *
11	Septicemia	Normal	0.094
12	Malnutrition, meningism	Normal	0.056
13	Lobar pneumonia	Normal	0.075
14	Gastroenteritis, bronchopneumonia; meningism	Normal	0.059
15	Myelogenous leukemia	Normal	0.118
16	Toxic psychosis	Normal	0.062
17	.....	Normal	0.0692
18	Malnutrition	Normal	0.0692
19	Tuberculous bronchopneupneumonia	Normal	0.08
20	Rickets	Normal	0.071
21	Gastro-enteritis, meningism	Normal	0.0134 *
22	Pneumonia, meningism	Pressure increased; otherwise normal	0.0674
23	Lobar pneumonia	Normal	0.088
24	Acute otitis media, pneumonia	Normal	0.0692
25	Empyemia	Normal	0.134
26	Malnutrition	Normal	0.065
27	Malnutrition	Normal	0.0786
28	Otitis media, meningism	Normal; 18 cells	0.064
29	Otitis media, meningism, pneumonia	No globulin; 11 cells; pressure much increased	0.0818
30	Pneumonia, acute parenchymatous, nephritis	Normal pressure +	0.0196 *
31	Acute gastro-enteritis, meningism	Normal pressure +	0.0592
32	Rickets, internal hydrocephalus	Normal	0.0588
33	Acute otitis media, meningism	Normal	0.075
34	Convulsions	Normal	0.066
35	Gastro-enteric intoxication, meningism	Pressure +; otherwise normal	0.1390 *
36	Cretinism, lobar pneumonia	Normal	0.0786
37	.....	Normal	0.063
38	.....		0.057
39	Malnutrition	Normal	0.1042

TABLE 1.—(*Continued*)

No.	Diagnosis	General Characteristics	Per Cent. Dextrose
40	Gonococcus, vaginitis	Pressure +; otherwise normal	0.066
41	Pertussis, meningism	Pressure +; otherwise normal	0.064
42	Septicaemia	Normal	0.091
43	Tetany	Normal	0.066
44	Pneumonia, meningism	Normal	0.085
45	Convulsions	Pressure +; otherwise normal	0.0486
46	Epilepsy	Normal	0.065
47	Rheumatic fever	Normal	0.094
48	.....	Normal	0.0836
49	Bronchopneumonia	Normal	0.1042

* Moribund.

TABLE 2.—Sugar Content of Cerebrospinal Fluid in Epidemic Cerebrospinal Meningitis

No.	Age Years	Dextrose Per Cent.	Remarks
1	11	*	Ill two days. Delirious.
		0.09	Second specimen. Following day intraspinal injections of antimeningococcic serum.
		0.08	Following day improvement.
		0.0868	
		0.0818	Great improvement.
2	⅓	0.0134	
		0.0134	Following day worse.
		0.0134	Death.
3	⅓	*	Condition poor.
		*	Seven hours later treated with serum. Recovery. Other specimens not obtained.
4	5½	*	Very ill. Treated with serum.
		0.036	Following day.
		0.0459	Following day.
		0.051	Fourth day. Great improvement. Recovery.
5	3½	*	Moderately ill. Serum treatment.
		0.0459	Improvement.
		0.059	Very much better. Recovery.
6	.....	0.075	Very ill. Serum treatment.
		0.058	Following day improved.
		0.062	Much better. Ultimate recovery.
7	.....	0.027	Very ill. Serum.
		0.065	Condition worse. Following day.
		0.04	Much worse. Death.
8	.....	*	Very ill.
		0.0362	No apparent improvement. Following day.
		0.05	Two days later. Much improved.
		0.057	Two days later. Much better. Recovery.

* Too small to determine.

TABLE 3.—Sugar Content of Cerebrospinal Fluid in Tuberculous Meningitis

No.	Age Years	Dextrose Per Cent.	Remarks
1	7	0.035	
		0.0324	Two days later.
		0.0674	Three days later. Tubercle bacilli in spinal fluid.
2	2½	0.0674	Autopsy. General miliary tuberculosis.
		0.0318	Tubercle bacilli in cerebrospinal fluid.
3	9		Autopsy. General miliary tuberculosis.
4	4	0.0454	X-Ray. General miliary tuberculosis.
5	4	0.0314	
		0.0338	Two days later.
		0.0334	Four days later. Tubercle bacilli in cerebrospinal fluid.
6	11	0.0294	Tubercle bacilli in cerebrospinal fluid. Autopsy. General miliary tuberculosis.
7	1 1/12	0.0330	First specimen.
		0.0380	Second specimen. Tubercle bacilli in cerebrospinal fluid.
8	2½	0.056	First specimen.
		0.0464	Second specimen. Tubercle bacilli in cerebrospinal fluid.
9	5½	*	First specimen.
		*	Second specimen.
		0.0370	Third specimen.
		*	Fourth specimen.
10	1 1/12	0.039	First specimen.
		0.022	Second specimen. Tubercle bacilli in cerebrospinal fluid.
11	5½	0.0718	Tubercle bacilli in cerebrospinal fluid.
12	4	0.022	First specimen. Tubercle bacilli in cerebrospinal fluid.
		*	Second specimen.
13	3	0.0426	Tubercle bacilli in fluid.
14	8	0.0402	First specimen.
		0.0318	Second specimen.
		0.0298	Third specimen.
		0.03518	Fourth specimen. Tubercle bacilli in cerebrospinal fluid.
15	2	0.0351	First specimen. Tubercle bacilli in fluid.
		*	Second specimen.
16	3½	0.0466	First specimen. Tubercle bacilli in fluid.
		0.0464	Second specimen.
17	8	*	Tubercle bacilli in fluid.
18	1⅓	0.038	First specimen. Tubercle bacilli in fluid.
		0.0240	Second specimen.
19	1¼	0.069	Tubercle bacilli in fluid.
20	5	0.059	First specimen.
		0.08	Second specimen.
		0.0588	Third specimen.
		0.0674	Fourth specimen.
		0.0606	Sixth specimen. Tubercle bacilli in cerebrospinal fluid.
21	4	0.0422	First specimen.
		0.0181	Second specimen. Autopsy. General miliary tuberculosis.
22	⅔	0.0422	First specimen.
		0.0261	Second specimen.
23	11	0.027	First specimen. Tubercle bacilli in fluid.
		0.0324	Second specimen.

* Too small to determine.

were obtained at the same time. In only two instances were the values similar. These results indicate that although the variations in the blood sugar and the cerebrospinal fluid sugar are practically identical yet there is no correspondence in the individual case at a given time.

TABLE 4.—CEREBROSPINAL MENINGITIS, MISCELLANEOUS TYPES

No.	Age Years	Disease	Dextrose Per Cent.	Remarks
1	1½	Pneumococcus meningitis	0.037	Five days' duration.
2	½	Influenza meningitis	*	First specimen.
			0.0214	Second specimen.
			0.022	Third specimen.
3	.....	Influenza meningitis	*	Moribund on admission
4	5½	Pneumococcus meningitis	0.0174	First specimen.
			*	Second specimen.
5	9	Streptococcus meningitis	0.0992	First specimen; fluid shows no cell or globulin increase.
			0.0718	Second specimen; seven cells per cubic mm.; no globulin.
			0.064	Third specimen; 156 cells; marked increase in globulin.
			0.0232	Fourth specimen; fluid cloudy; many pus cells.

* Too small to determine.

TABLE 5.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN POLIOMYELITIS AND POLIO-ENCEPHALITIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	5/12	0.063	Subacute stage. Anterior poliomyelitis.
2	5	0.0588	First specimen. Acute stage poliomyelitis.
		0.065	Second specimen.
3	.....	0.088	Chronic stage. Duration two weeks.
4	.....	0.0376	Acute polio-encephalitis. First specimen; 830 cells.
		0.0426	Second specimen; 750 cells.
		0.0398	Third specimen.
		0.0394	Fourth specimen; 170 cells.
		0.0395	Fifth specimen.
		0.044	Sixth specimen; 40 cells.

Of interest are the results from four patients who were moribund at the time of examination. In three instances the dextrose value was very low; in one it was high.[11]

The Sugar Content of Cerebrospinal Fluid in Cases of Epidemic Cerebrospinal Meningitis.—Eight cases of meningococcic meningitis were observed and are described in Table 2. In common with the results of Connall, DuBois[12] and others we found that the reducing agent is usually greatly decreased. Connall states that the reducing power usually increases with improvement of the patient. This is well shown in Cases 1, 4, 5 and 8. In Case 6, however, there was a normal sugar value at the height of the disease and no increase with improvement. Patient 7 showed an increase in the reducing action of the cerebrospinal fluid despite the fact that he became progressively worse.

TABLE 6.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN CEREBROSPINAL SYPHILIS

No.	Age Years	Dextrose Per Cent.	Remarks
1	.....	0.060	Case 3, Table 7, Wassermann positive on blood and cerebrospinal fluid. Idiocy.
2	.....	0.059	Hydrocephalus. First specimen.
		0.0558	Second specimen.
		0.0592	Third specimen.
		0.0514	Fourth specimen.

The Sugar Content of Cerebrospinal Fluid in Cases of Tuberculous Meningitis.—A number of observations have been published concerning qualitative tests of the reducing power of cerebrospinal fluid in cases of tuberculous meningitis. The results are inconstant, but in a large percentage of the cases the fluid was capable of reducing copper salts (Connall, DuBois and others). In consideration of these results, our quantitative determinations are of special interest. (Table 3.) We found that in a single specimen of spinal fluid the dextrose percentage may be normal, slightly reduced or greatly reduced and this variation could be traced to no definite influence. In most of our cases, however, there was a decrease in the sugar value at some stage of the disease and usually as the disease progressed. To this there were only two marked exceptions. In Case 1 the sugar was decreased at the time of the first tap but at the time of the third

11. These cases are cited in Table 1, but can scarcely be considered normal.
12. Du Bois: Summary of Four Years of Clinical and Bacteriological Experience with Meningitis in New York City, AM. JOUR. DIS. CHILD., 1915, ix, 1.

was normal. In Case 20 the sugar was normal during the entire course of the disease.

Miscellaneous Types of Meningitis.—Cerebrospinal fluid from two cases of pneumococcus meningitis, two cases of influenza meningitis and one of streptococcic meningitis were examined. In all the reducing power was greatly decreased or absent. Case 5 is of sufficient interest to cite. The patient, a boy of 8 years, was affected with septicemia due to streptococcus pyogenes. The first specimen of cerebrospinal fluid was normal in cell content, globulin and sugar. The patient gradually developed symptoms of meningitis and with their progression the sugar content of the cerebrospinal fluid became less, and at the time when the symptoms were marked, was greatly reduced.

TABLE 7.—SUGAR CONTENT OF CEREBROSPINAL FLUID IN CASES OF IDIOCY

No.	Age Years	Dextrose Per Cent.	Remarks
1	4	0.10	Idiocy and congenital syphilis.
2	.....	0.0692	Idiocy. Epilepsy.
3	11	0.061	Case 1, Table 6. Idiocy; syphilis.
		0.06	Second specimen.
		0.075	Third specimen.
4	.....	0.0514	Wassermann on blood positive; spinal fluid negative.
5	.....	0.066	Idiocy; spastic paraplegia.
6	.....	0.064	

Poliomyelitis and Polio-Encephalitis.—In three cases of poliomyelitis the reducing power of the cerebrospinal fluid was normal. In one case of polio-encephalitis the sugar was decreased.

Idiocy. Congenital Syphilis.—Two cases of cerebrospinal syphilis and six cases of various types of idiocy were observed. In all the sugar content of the cerebrospinal fluid was within the limits of normal.

IV. SUMMARY

1. The reducing substance in cerebrospinal fluid is a fermentable, dextrorotatory sugar, probably dextrose.

2. In infants and children free from meningeal disease the cerebrospinal fluid sugar ranges from 0.05 to 0.134 per cent. (dextrose), approximately the same figures which obtain for blood sugar.

3. There is no decrease in the reducing power of the cerebrospinal fluid in meningism.

4. A large proportion of the cases of tuberculous meningitis show a decrease in the sugar content of the cerebrospinal fluid at some stage of the disease. In a few cases, however, the sugar is normal at all times or diminished but slightly. A decrease only is of diagnostic value.

Our material was obtained from the service of Dr. L. E. La Fétra at Bellevue Hospital. We desire to express our indebtedness for this privilege and for encouragement in the work. To Dr. Charles Norris, Director of the Pathological Laboratory, we are indebted for his kindness in placing the facilities of his laboratory at our disposal.

FAMILIAL SYPHILIS*

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During the past few years at the St. Louis Children's Hospital it has been our custom to follow all cases of syphilis coming for treatment, and in addition to investigate the remainder of each patient's family in regard to the occurrence of syphilitic infection. In this paper some of the results of this familial study are given. There has been no selection of cases or families, other than that those records have been analyzed in cases in which the investigation was more or less complete.

Except in three instances of second marriages, and possibly one other, in the 100 families studied, the father was apparently the first infected. In the three second marriages the mother was apparently infected by her first husband.

SYPHILIS IN THE MOTHERS OF SYPHILITIC CHILDREN

Whether or not the mother of a syphilitic child is necessarily infected has been a much disputed point. In the families studied in addition to the history, Wassermann reactions were made on eighty-five mothers of syphilitic children. These were positive in seventy-three instances (85.9 per cent.) while twelve mothers gave a negative Wassermann reaction. Of the twelve mothers who gave negative Wassermann reactions the interval between the birth of their last child with positive reaction and the examination was two months, five months, nine months, three years, four years, seven years, seven years, ten years, twelve years, thirteen years, thirteen years and thirteen years. The mother examined at two months' interval had evidence of active syphilis at the time of examination; so strong that the result of the Wassermann was doubted. She also gave a history of a primary lesion one year previously, with treatment. The one at five months also gave a positive history of infection. The one at nine months had been under a physician's care for some time before being examined by us and may have had treatment. She states that blood tests were made and medicine given. The one at three years was accidentally poisoned seriously and almost fatally with arsenic about

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* From the Department of Pediatrics of the Washington University Medical School and the St. Louis Children's Hospital.

* Read in part before the St. Louis Medical Society, May 29, 1915.

one year previous to the test. The one at four years is presumably a prostitute. One at seven years had Hutchinson's *teeth*. The other at seven years gave a history of an initial lesion and a short course of treatment eight years previously. The remainder of the patients gave no evidence or history of infection.

Up to an interval of four years, then, those mothers who gave negative Wassermann tests, gave either a history of infection or of treatment or both. After four years one gave a history of infection and treatment and another had Hutchinson's teeth. This leaves but six cases (four years, ten years, thirteen years, thirteen years and thirteen years) to whom no such suspicion is attached, and with the exception of the four-year case (presumably a prostitute) these mothers were examined at least ten years after the birth of their last syphilitic child.

It is easily conceivable that these mothers had had syphilis but that the infection had quieted to the extent of a negative Wassermann by the time they were examined. It would seem that a syphilitic infection really does have a tendency to die out, as does also its transmissibility to children, as will be shown later. Four of these mothers with negative reaction have borne children with negative reactions by the same father since their last child with positive Wassermann, which is further evidence that the infection is dying out. It is also significant that, though in all but two cases the syphilis in this group of mothers was presumably latent, 86 per cent. gave a positive Wassermann, while most figures given for latent syphilis are much lower than this. The whole proof of germinal transmission lies in the supposed fact that women who are free from syphilis can give birth to syphilitic children. This is no proof whatever because it can not be proved that these mothers have not been infected. Warthin has demonstrated at necropsy *Spirochaete pallida* in the viscera of patients who before death gave a negative Wassermann reaction.[1]

It is recognized by abundant and good authority that a negative Wassermann does not mean the absence of syphilis. The Wassermann reaction is looked on merely as one of the symptoms of syphilis, but it is the most constant symptom, and in active syphilis it is negative only under fairly definite circumstances. On the other hand, to assert that a positive Wassermann invariably meant syphilis, would be unwise, for it is authoritatively asserted that it may be positive in certain cases of scarlet fever, leprosy, scleroderma, yaws, carcinoma and malaria. These diseases can usually be ruled out, however, and in their absence a positive Wassermann constitutes a valid proof of syphilis and indi-

1. Warthin, A. S.: Personal communication.

cates that the infection is actually present at the time of examination and is not due to syphilis in the past.

One of the mothers having a positive Wassermann refused treatment because there was nothing the matter with her and never had been. She returned a year later with tertiary lesions in her nose and throat. Rabbits have been successfully inoculated from the blood and milk of latent syphilitics whose only symptom was a positive Wassermann.[2] We also know that in certain cases of paresis and tabes the interval between the initial lesion and these affections may be thirty to forty[3] years. Colles' law, that a syphilitic child even though it have lesions in the mouth never causes syphilis of the mother's breasts, has been abundantly proved. But the mother remains unaffected not because she is immune, but because she has the disease.

It is interesting to note that of the group of eighty-five mothers, seventy-four (87 per cent.) deny all knowledge of the infection, nor do they give any history other than of abortions which can be interpreted as symptoms of syphilis. Of those who give positive Wassermann reactions, sixty-seven out of the seventy-three give a negative history. This negative history can not be used as strong evidence against infection, for in women showing active lesions of syphilis more often than not, no chancre has been seen.[3]

SYPHILIS IN THE FATHERS OF SYPHILITIC CHILDREN

In most of the fathers of this group the infection was latent at the time of marriage, and a relatively small number give a history of active symptoms after marriage. Evidence is accumulating that spirochetes localize early in the testicle, even though they may not produce active lesions at this point. Nichols[4] states that "experience has shown that the testicle rarely escapes." Warthin[1] states that in his necropsy material there were active lesions in the testis in all cases of latent syphilis. This would easily explain how an apparently healthy father can infect his wife. In such a case there would be a contact exposure just as surely as if a primary lesion existed.

SYPHILIS IN THE OFFSPRING OF SYPHILITIC PARENTS

As the result of syphilis numerous families remain sterile. The figures for sterility vary from 10 per cent. to 30 per cent., depending on the material studied. When there is an embryo there is a variety of fates to which it may come. Many marriages result only in abor-

2. Heiman: Jour. Am. Med. Assn., 1915, lxiv, 1463.
3. White: Jour. Am. Med. Assn., 1914, lxiii, 459.
4. Nichols: Jour. Am. Med. Assn., 1914, lxiii, 466.

tions (nearly 13 per cent. in Haskell's material[5]). Since the starting point in our material was a syphilitic child, we have no data bearing on this phase.

Among our syphilitic patients all the living children of 100 families have been examined, Wassermann tests made and the family history studied. In these 100 families there were 331 pregnancies. Of these 100 (30.2 per cent.) were abortions, 31 (9.3 per cent.) still births and 200 (60.4 per cent.) living births. Of the 200 living births 35 children died early and 4 died late, and 161 remained alive and were examined. Of these, 12 are now dead. Of the 35 who died early, 5 gave an undoubted history of syphilis and a number gave suspicious histories. Of the four who died late, one was an idiot. Of the 161 examined, 107 were clinically positive and had positive Wassermann tests. Five were clinically positive and had negative Wassermann reactions. Sixteen, who showed no evidence of syphilis, gave positive Wassermann reactions. Thirty-three, who gave no clinical proof of syphilis, gave a negative Wassermann reaction.

Of the five who were clinically positive but gave negative Wassermann reactions, one was a young infant who had snuffles and a large spleen. The mother and sister both gave a positive history and a positive Wassermann reaction. Shortly after beginning treatment the baby developed a syphilitic rash. The baby was removed from the hospital and a second Wassermann was not done. The second case was a nursing baby. The mother had active syphilis and was taking treatment. The baby had an active process in the nose. The third case was a 7-year-old girl who had a markedly sunken nose and who for that reason was the starting point for investigating that family. Both the mother and younger brother gave a positive Wassermann. The fourth case was a 4-year-old girl whose mother and younger sister were both positive and the patient had a general rash which was thought to be syphilitic. The fifth case was a 3-year-old boy with a positive history, and who had had some treatment. His mother and younger brother both had syphilis.

A negative Wassermann reaction is obtained in the presence of active syphilis only under certain definite conditions. As had been noted in cases not of this series, very young babies, even with undoubted active syphilis, not infrequently give a negative Wassermann. It has also been noted that even small amounts of mercury tend to cause a positive blood to react negatively.

H. Boas[6] states that of fifty-seven babies of syphilitic mothers giving negative Wassermann reactions at birth, thirteen during a

5. Haskell: Jour. Am. Med. Assn., 1915, lxiv, 890.
6. Quoted by Haberman: Jour. Am. Med. Assn., 1915, lxiv, 1146.

three months' period of observation developed syphilitic manifestations and a positive Wassermann, and two others showed syphilitic changes at necropsy, having had no manifestations during life.

LATENT SYPHILIS

It is seen that 10 per cent. of the children examined had latent syphilis, i. e., a positive Wassermann and no clinical evidence of syphilis. One of these children gave a history of epiphysitis at 3 months. Other than this no early history was acknowledged by any of the mothers. The question naturally arises, Are these children actively infected with syphilis? When we inquire into the history of those showing late manifestations, we frequently find, so far as obtainable history is concerned, that there has been no previous warning that the disease existed. One of our patients developed, as her first known symptom, an interstitial keratitis at 20 years. We know that the spirochete can lie dormant much longer than this and then manifest itself. One patient of this latent group who had taken very irregular treatment for about a year and who had never had previous manifestations, recently developed an active lesion in the throat. Another developed an interstitial keratitis after about two months of antisyphilitic treatment. A positive Wassermann reaction in these apparently healthy children has the same significance that it does in the parent, and it is our belief that the children in this group are actively infected.

The fact that there are thirty-three children, 10 per cent. of the total pregnancies, who show no evidence of syphilis, and at the same time give a negative Wassermann reaction, is rather hopeful. Yet the pleasure to be taken in this fact is not altogether unalloyed. In this small group there were two mental defectives and an idiot, and it is impossible to say that all of this group are free from syphilitic infection. In one instance, one such negative child returned about a year after his original examination with a tertiary type of lesion and a positive Wassermann. Though no classification of those in this group showing stigmata of degeneration was attempted, it can be truthfully stated that a goodly proportion did show degenerative influences, either physical or mental.

TOTAL SYPHILIS IN THE FAMILIES STUDIED

In summing up the total syphilitic infection in these families, we find that where marital relations are uninvolved, all of the fathers and probably all of the mothers have been infected. Presuming that the abortions, stillbirths, all of the early deaths and at least one of the late deaths were due directly or indirectly to syphilitic infection,

syphilis among the offspring amounts to 89 per cent. of the total pregnancies, and total syphilis in the family amounts to 93 per cent. of all its members.

DECREASING GRADES OF INFECTION IN THE OFFSPRING

In 1876 Kassowitz announced the general rule that the degree of transmissibility of syphilis gradually diminished in proportion to the duration of the disease. The first pregnancies are likely to be early abortions followed by late abortions and stillbirths, then by living children with decreasing grades of infection, and finally by normal children. Our series shows that any one family does not necessarily go through this list from the beginning, but may start from any one point and from there on continue with the decreasing infection. The start may be even as late as healthy children, as in one family now under observation.

In studying this series we find that this rule remains on the whole correct. In many cases it would seem as if there is a general tendency for the infection to die out both in the parent and in the child, or at least to localize in the mother in places where it is not readily transmitted to the fetus. This would explain the nonsyphilitic children of a mother with latent syphilis. In sixty-nine of our families in which the order of pregnancies was ascertained and all of the living children examined, forty-four families followed Kassowitz's rule and twenty-five varied more or less from it. If in four families the first child, being apparently nonsyphilitic, could be excluded on the ground that the mother was not yet infected, these families would otherwise have followed the rule. In no case was there a complete reversal of the rule, but in one family there was first a nonsyphilitic child, then a negative child with a positive Wassermann, followed by seven stillbirths and then a living birth in which the child was syphilitic. Nonsyphilitic children were interspersed between syphilitic children in seven instances in five families. For the most part the variation from the rule consisted of abortions following living syphilitic children, so that in a large measure in these twenty-five irregular families Kassowitz's rule was followed.

It has been thought by some, but not proved, that the more intense the disease in the parent the less severe it is in the surviving children. This does not appear to be the case. So far as we have been able to determine in this study, the starting point in Kassowitz's scheme is not determined so much by the severity of the infection in the parent as by the length of time elapsing between the infection and the first pregnancy. It has frequently been stated that the infection is much more probable and more severe in the children if the mother and not

the father is diseased. We believe the evidence shows that all mothers of syphilitic children have been infected, and it is quite reasonable that the infection in the child is more likely if the infection in the mother is active to the point of recognition than if it were not.

NONSYPHILITIC CHILDREN OF SYPHILITIC MOTHERS

In eight families of this group there are twelve apparently nonsyphilitic children who follow syphilitic children and whose mothers still give positive Wassermann reactions. That the infection in the mother has become localized in such places that it is difficult of transmission to the offspring, would seem to be a reasonable explanation. Nor do these children necessarily prove immunity on the part of the child. They probably do not acquire it from the mother after birth for the same reason that they do not before birth, viz., its localization in unexposed parts.

EVIDENCE OF A NEUROTROPIC STRAIN OF SPIROCHETE

The idea that there are various strains of spirochete is becoming more and more established. Some seem to think the variations are a matter of the race of people infected and their racial reaction to the infection. This, however, does not seem to be true. Inland in China syphilis is common, but parasyphilis is quite rare; but in the Chinese who have brought syphilis from other countries or who have acquired it in coast ports, the incidence of parasyphilis is similar to that in this country.[7] The greatest support of the idea of different strains of spirochete is based on its apparent predilection for the nervous system in certain groups with the same infection and the relative absence of this predilection in other groups with the same infection. In the families of this series this is shown very strikingly in a few instances.

FAMILY I. W.—Father has paresis. Mother recently had tertiary lesions in her nose and throat. First and third children have cerebrospinal syphilis. The second child recently had tertiary lesions in her throat.

FAMILY C. M.—Father died of paresis. Mother gives a positive Wassermann. First pregnancy resulted in a miscarriage, second a stillbirth, and of the third the child has cerebrospinal syphilis.

FAMILY H. W.—Father well. Mother has paresis. Four miscarriages. First living child died of convulsions at 9 days. Second and third children have cerebrospinal syphilis.

FAMILY W. B.—Father died of aneurysm. Mother well. First pregnancy resulted in a stillbirth. The child born of the second is 14 years old, gives a positive Wassermann reaction and is hysterical. The third pregnancy resulted in a miscarriage. The child of the fourth has cerebrospinal syphilis. Children of the fifth and sixth are mentally deficient, but give a negative Wassermann reaction.

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7. Reed: Jour. Am. Med. Assn., 1915, lxiv, 1383.

In the remaining six families in which cerebrospinal syphilis appears in the child there are but eight living births. None of the others had so far developed this manifestation. One of the fathers committed suicide.

MISCELLANEOUS OBSERVATIONS

In three families we have what is apparently an infection of the mother by the first husband and a failure of the mother to infect the second husband in two instances, and in the third he was not infected until seventeen years after marriage. This observation was based on histories and Wassermann tests on the families as they exist at present. In each instance the mother continued to bear syphilitic children in the second marriage. In two instances the mother denied any knowledge of the disease.

One family deserves especial mention for the long period of infectivity of the mother. The father was infected before marriage. The mother denies all knowledge or symptoms of syphilis. The child of the first pregnancy is now 20 years old and very recently developed an interstitial keratitis, with no previous manifestation, and gives a positive Wassermann reaction. This child was followed by three miscarriages and six living births, two of which children died in early infancy. The remaining four, the youngest being 2 years old, all give positive Wassermanns, and two of these show manifest syphilis. The mother has taken no treatment and now gives a strongly positive Wassermann reaction.

Though there are several mothers in this group with signs commonly seen in hereditary syphilis, this series offers no proof one way or the other as to the transmissibility of syphilis to the third generation. Clark[8] has reported a case of acute visceral hereditary syphilis in a 24-year-old woman. These late cases are not rare. I see no good reason why it is impossible for the 20-year-old girl mentioned above or Clark's 24-year-old patient to transmit syphilis to offspring. Such an event is not only possible, but in a very small number of cases probable.

SUMMARY

Germ transmission of hereditary syphilis has not been proved, and it does not seem likely that it ever occurs.

It is highly probable that all the mothers of syphilitic children have been infected with syphilis. Of eighty-five mothers of syphilitic children 86 per cent. gave positive Wassermann reactions. All of the remaining cases but six gave a history of infection or treatment, or both. Five of these six patients were examined at least ten years after

8. Clark: Jour. Am. Med. Assn., 1914, lxii, 1167.

the birth of their last syphilitic children and the infection is probably dying out.

Eighty-seven per cent. of the mothers deny all knowledge of the infection. The mothers are for the most part infected during the latent stage of the father.

Of 331 pregnancies in 100 families, 30 per cent. were abortions, 9 per cent. stillbirths, 61 per cent. living births. Of the living births 24 per cent. had died. Of those living 80 per cent. had syphilis.

Of the total pregnancies 90 per cent. were presumably syphilitic and although 10 per cent. seem free from syphilis, there is no proof that they all are. The total syphilis in these families amounts to 93 per cent. of the entire family.

For the most part our families followed Kassowitz's rule; i. e., decreasing grades of infection in the children.

In case of syphilitic mothers bearing nonsyphilitic children, it is probable that the infection in the mother is localized in places where it is not readily transmitted.

The idea that there are different strains of spirochetes receives some support from these families.

Transmission to the third generation, though not proved, is distinctly an occasional probability.

SOME INTERESTING FACTS PLAINLY BROUGHT OUT BY A CHART METHOD OF STUDYING AND MANAGING CASES OF DIABETES MELLITUS IN CHILDREN*

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Charts give one in the easiest and quickest way a fund of information concerning a case. In many febrile diseases valuable impressions are often gained if the whole course of the temperature is before one's eyes. This applies to diseases of long duration, such as diabetes mellitus, if it can be simply charted. This can be done, and the ones I show contain all the information necessary, and yet are not too cumbersome. They tell you what you have done, when you did it, and the results.

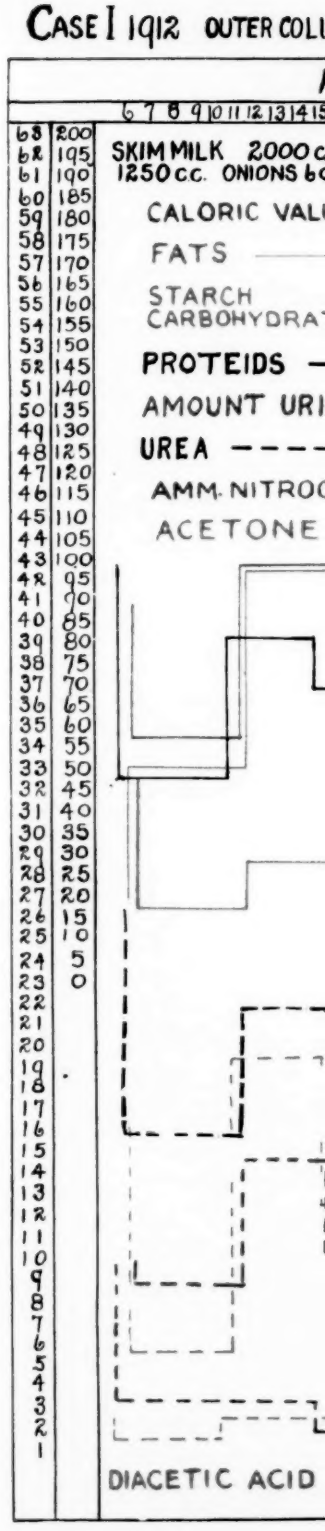
The upper half of my charts shows in unbroken lines the number of grams of the three food elements ingested, and their total caloric value. The lower half shows in broken lines the urine analyses, and hence the condition of your patient on the selected diet.

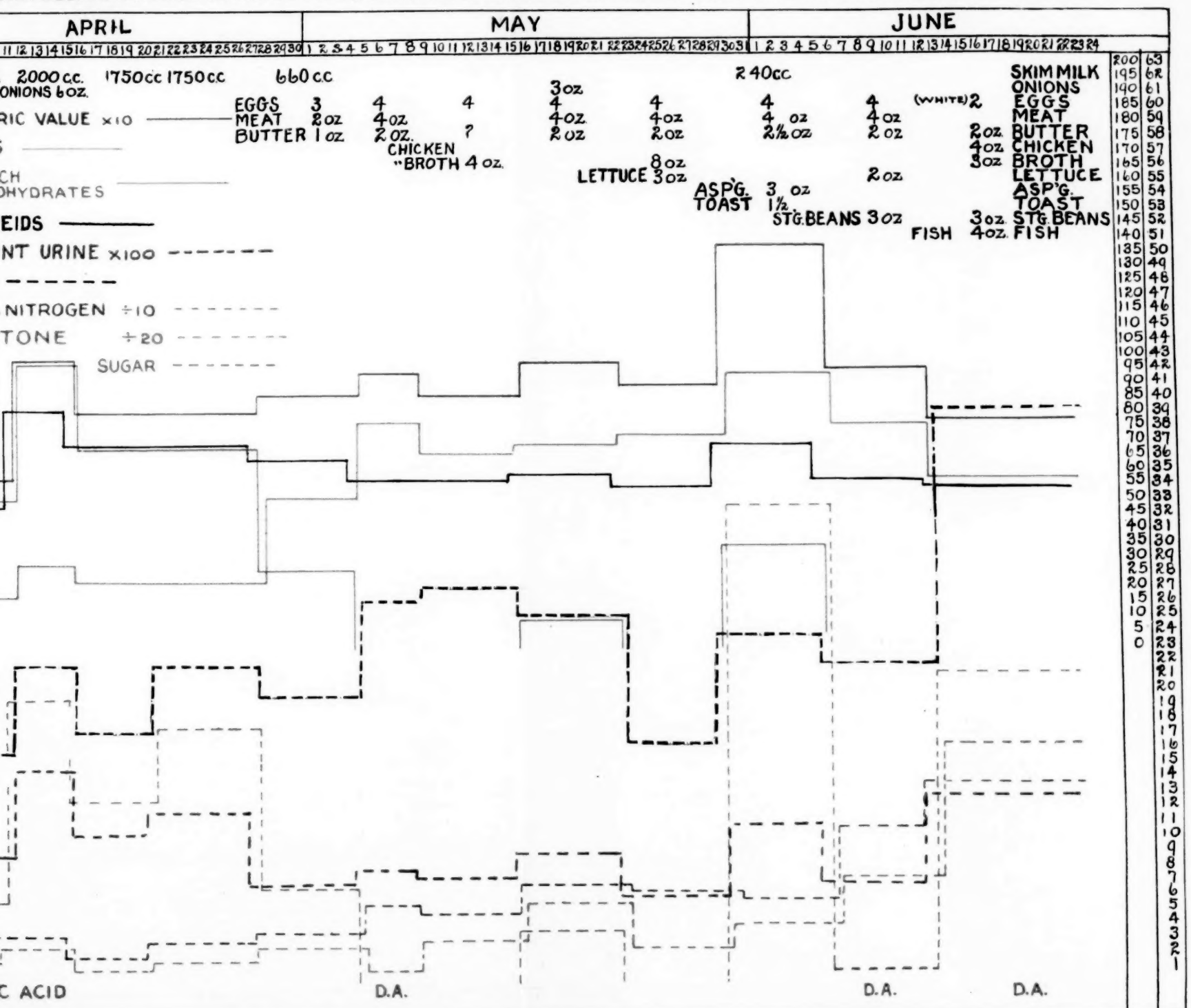
For further ease of reading, colored crayons are used. The continuous red line above shows the number of grams of carbohydrates ingested, and the lower broken red line shows the amount of sugar in the urine. The upper broken black line shows the proteins ingested, and the lower broken line the amount of urea.

The unbroken lines above of violet and blue show, respectively, the amount of fat ingested, and the caloric value of the diet. The broken lines below in brown, green and violet show the amount of urine, of ammonia-nitrogen, and of acetone eliminated. To save breadth of chart the figures on the side line must be multiplied by 100 for the amount of urine. Because the amount of ammonia-nitrogen and acetone are too small for charting purposes they must be multiplied by ten and twenty, respectively, and then charted. With these few points of explanation understood one can at a glance grasp the whole situation.

In the first chart shown skimmed milk was first given, because we were told the child of eight years could not easily tolerate fats. This allowed us very definitely to study her carbohydrate tolerance in the form of milk sugar. Because the amount of sugar fell on skimmed milk from 27 gm. in the first twenty-four-hour sample to 5.5 gm., we definitely learned that her milk sugar tolerance was poor. Not till all the milk was prohibited was she sugar-free. We learned, as shown,

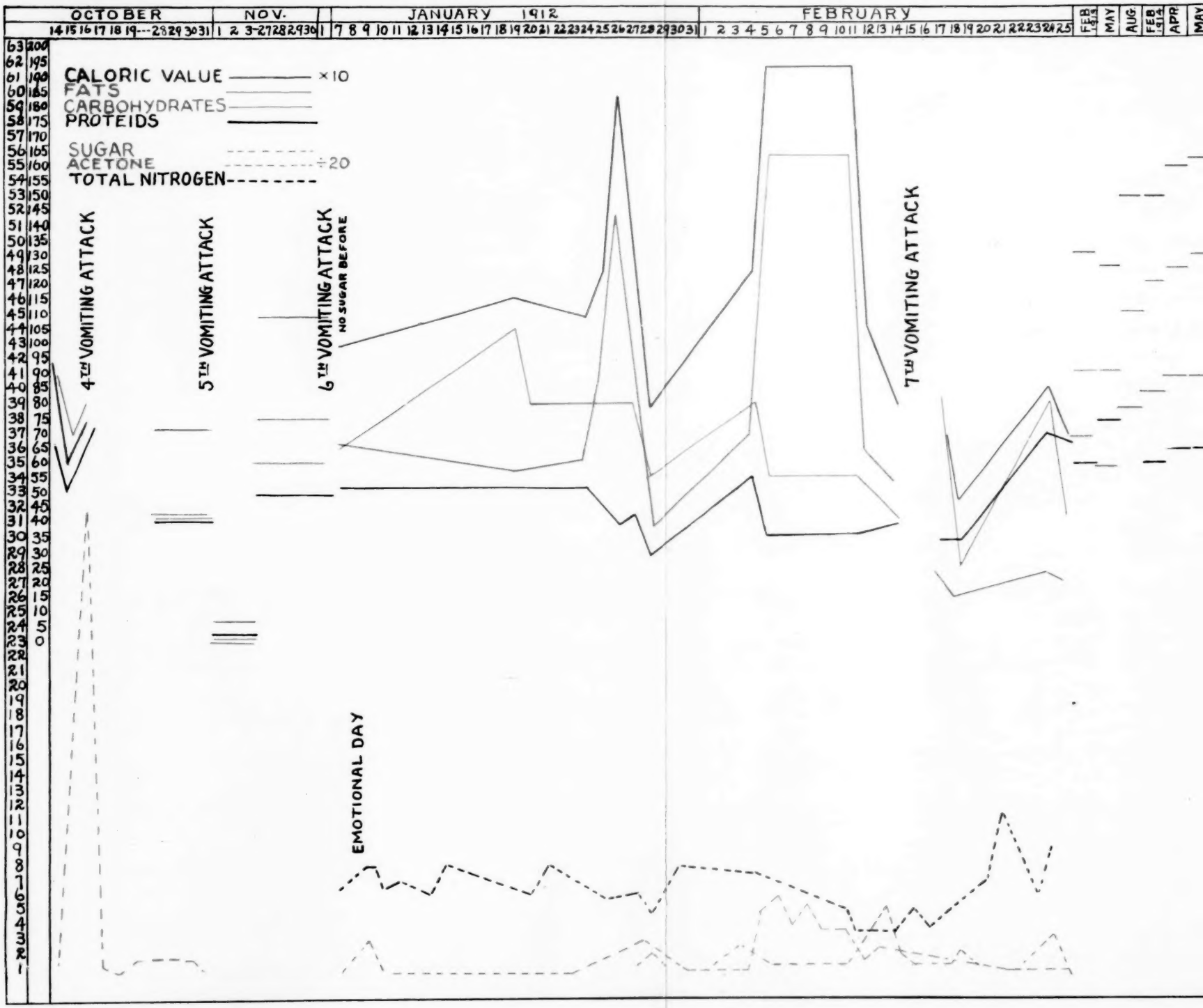
* Read at the meeting of the American Pediatric Society, Lakewood, N. J., May, 1915.

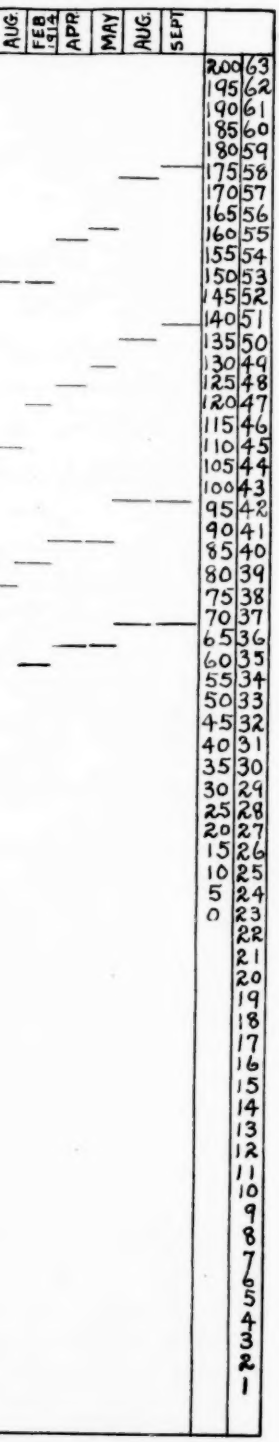




Illustrating Article by DeWitt H. Sherman, M.D., American Journal of Diseases of Children, January, 1916.

CASE II 1911. OUTER COLUMNS OF FIGURES REFER TO LOWER ½ CHART AND ARE GM. OR C.C. INNER COLUMNS REFER TO UPPER ½ CHART AND ARE GM. OR





that she could be sugar free on meat, eggs, and butter, but as soon as a fodder food, such as onions, was given, she passed 4/10 as much sugar in the urine as she had ingested carbohydrates in the onions. While she tolerated meat and eggs well, when fish was added the amount of sugar which appeared was about 1/6 of the amount of fish ingested. This was peculiar.

The acetone was always present and gradually increased on all diets given. This alone showed, that in spite of the fact she was sugar-free, she was losing ground. As the acetone increased so did the ammonia-nitrogen, and this was another sign of unfavorable progress.

As regards Chart 2, the following points are of interest: With neurotic tendencies and a precocious intellect, this girl of 10 years was a victim of cyclic vomiting. We have charted four attacks of vomiting, and before three of these sugar appeared. Naturally it quickly disappeared on the starvation of persistent vomiting. It has consequently occurred to me that in cases of cyclic vomiting we might find sugar just before an attack more often than we suspect, due probably to the same faulty metabolism, which causes the vomiting. We tested the fat tolerance twice, as shown on the charts. The first time we gave 145 gm. and promptly sugar appeared. The second time we gave 165 gm. per day for six days. Soon sugar (2.50 gm.) appeared and decreased to 1.00 gm., when the carbohydrates were reduced much below a well known carbohydrate tolerance. After the high fats were lowered below a well known tolerance, the sugar not only persisted but rose to 5 gm., and she had a vomiting attack. This late rise in sugar and the vomiting were then, without doubt, due to the damage done by the fats. I could then conclude, (1) that an excess of fat may in itself cause sugar to appear, and (2) that high fat may be a cause of cyclic vomiting.

This second statement has been proved in her case, because, since her fats have been kept at 100 gm. or less per day, she has not vomited. As regards the acetone, the fats caused it to increase.

I mentioned above that the child was a neurotic. One day, as shown, sugar appeared while we were testing the carbohydrate tolerance. As no clear cause was seen we kept on increasing the carbohydrates, and in spite of this increase the sugar disappeared. On very thorough investigation we learned that the sugar was undoubtedly due to the worry of a guilty conscience, because she had been for weeks doing something she knew was not right. This shows that an unbalanced nervous system can produce sugar.

The chart in her case shows no idiosyncrasy to any of the different starches, proteins, or fats. They were all equally tolerated. Her tolerance to milk sugar in milk and levulose in fruits was only fair, and no different from any other starch.

The third chart I do not show. At varying intervals I give the usual starvation or water day. This boy of four years on one of these days vomited, with nervous manifestations, going into more or less of a stupor. This I experienced once in another child, except that the second child was delirious. No cause have I found for such an upset in either case.

SUMMARY

Charts aid materially in the study of a case of diabetes.

In one of my cases sugar was caused (1) by high fats, and (2) by mental anxiety.

In another, fish caused sugar, while all the other proteins were fairly well tolerated.

In one case high fats caused cyclic vomiting.

Sugar may appear before cyclic vomiting attacks more often than we suspect.

THE ETIOLOGY OF PACHYMENINGITIS HEMORRHAGICA INTERNA IN INFANTS*

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Since the first accurate description of pachymeningitis hemorrhagica interna by Virchow[1] in 1856, observers have differed in their views regarding the exact nature of this condition. Virchow believed that the membrane formation on the inner surface of the dura precedes the hemorrhage. Huguenin[2] maintained that the hemorrhage is primary, the organization of the clot causing the membrane formation. The work of Melnikow-Raswedenkow[3] and others supported Virchow's view, which has gradually become the prevailing one.

It was thought that most of the cases seen in the adult[4] resulted from sclerotic changes incident to chronic diseases of the brain, heart, kidneys and lungs. Similarly, regarding cases occurring in the infant, the prevailing opinion seemed to be that pachymeningitis is secondary to other diseases, the cerebral changes being usually discovered at necropsy in infants dying from various infectious diseases, or in chronic cachectic conditions.[5]

Kremiansky[6] performed experiments on dogs, showing the importance of alcoholism as an etiologic factor in the production of this disease. Needless to say, cases occurring in infancy cannot be explained by this hypothesis.

It has been maintained by many observers that cerebral hemorrhage occurring at birth is an important factor in these cases. Recent workers though emphasizing other factors in adults, still attribute to

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* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

1. Virchow, Rudolf: Das Hämotom der Dura Mater, Verhandl. d. phys. med. Gesellsch. in Wurzburg, 1857, vii, 134.
2. Huguenin, G.: Handbuch d. Speciellen Pathologie und Therapie (Ziemmsen), 1876, xi, 342.
3. Melnikow-Raswedenkow, N.: Histologische Untersuchungen über den normalen Bau der Dura Mater und über Pachymeningitis interna, Beitr. zur path. Anat. u. zur allgemeinen Path. (Zeigler), 1900, xxviii, 217.
4. Ciarla, E.: Beitrag zum pathologisch anatomischen u. klinischen Studium der Pachymeningitis cerebralis hemorrhagica, Arch. f. Psychiat., 1913, lii, 439.
5. Holt, L. Emmett: Diseases of Infancy and Childhood, New York, 1913, p. 698. Steffen, A.: Handbuch d. Kinderkrankheiten, Tubingen, 1880, v, 380.
6. Kremiansky, J.: Ueber die Pachymeningitis interna hemorrhagica bei Menschen und Hunden, Virchow's Arch. f. path. Anat., 1868, xlii, 129 and 321.

such hemorrhage great importance in the production of this disease in infants.[7]

Boeckmann[8] made a study of numerous cases coming to necropsy following various cranial operations. Most of these had had considerable hemorrhage following the operation. In no case could Boeckmann demonstrate any pachymeningitis; its absence, he thinks, disproving the importance of trauma as a cause for pachymeningitis.

Marie[9] and his co-workers were unable to produce pachymeningitis hemorrhagica in dogs and rabbits by the subdural injection of blood.

In a series of 5,998 necropsies on children, Kowitz[10] found intracranial hemorrhage present in 16.9 per cent., pachymeningitis in only 3.9 per cent. Among other causes given for this disease are syphilis,[11] scorbutus,[12] hemorrhagic diseases,[13] and pertussis.[7]

Some observers[14] have laid more or less stress on digestive disturbances in infancy as of possible etiologic significance, while others[15] have noted that cases are occasionally brought to a hospital on account of alimentary symptoms, which often obscure the true nature of the disease.

The possibility of pachymeningitis being the result of a hematogenous infection is suggested by the case reported by Schottmüller[16] of a woman 28 years old who died following a puerperal septicemia of streptococcus origin. The fluid obtained by lumbar puncture during life showed an excess of globulin, the cell count was 181, cultures

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7. Hada, B.: Ueber die gehirnkomplikationem des Keuchhustens mit besonderer Berücksichtung der Pachymeningitis productiva interna, Virchow's Arch. f. path. Anat., 1913, ccxiv, 206. Wohlwill, F.: Ueber Pachymeningitis hemorrhagica interna, Virchow's Arch. f. path. Anat., 1913, ccxiv, 388.

8. Boeckmann, M.: Ein Beitrag zur Ætiologie der Pachymeningitis interna hemorrhagica, Virchow's Arch. f. path. Anat., 1913, ccxiv, 380.

9. Marie, P.: Roussy, G., and Laroche, G.: Sur la reproduction expérimentale des pachyméningites hemorragiques, Compt. rend. Soc. de biol., 1913, lxxiv, 1303.

10. Kowitz, H. L.: Intrakranielle Blutungen und Pachymeningitis hemorrhagica chronica interna bei Neugeborenen und Säuglingen, Virchow's Arch. f. path. Anat., 1914, ccxv, 233.

11. Heubner, O.: Pachymeningitis hemorrhagica bei hereditarer Syphilis, Virchows Arch. f. path. Anat., 1881, lxxxiv, 267.

12. Sutherland, G. A.: On Hematoma of the Dura Mater Associated with Scurvy in Children, Brain, 1894, xvii, 27.

13. Oppenheim, H.: Lehrbuch d. Nerven krankheiten, Berlin, 1908, p. 849.

14. Misch, P.: Zwei Fälle von Pachymeningitis hemorrhagica interna, Jahrb. f. Kinderh., 1905, lxii, 229. Poulet, Anna: Ein fall von Pachymeningitis nicht traumatischen natur im Kindesalter, Inaug. Dissert., Zurich, 1902.

15. Göppert, F.: Drei Fälle von Pachymeningitis hemorrhagica mit Hydrocephalus externus, Jahrb. f. Kinderh., 1905, lxi, 51. Meigs, Grace: Jour. Am. Med. Assn., 1913, lxi, 2186.

16. Schottmüller, H.: Pachymeningitis interna infectiosa acuta und Meningismus, München. med. Wchnschr., 1910, lvii, 1984.

were sterile. Postmortem examination revealed a pachymeningitis. Göppert thinks that Krücke's[17] case of pachymeningitis demonstrated in a child dying from pharyngeal and laryngeal diphtheria illustrates a similar possibility. Krücke's case lacks the clinical history prior to death, nor was Krücke able to demonstrate diphtheria bacilli in the lesions, attributing his failure to the fact that the necropsy was not done until sixty hours after death.

Until recently there were few cases of this disease reported in infancy. Finkelstein[18] and Göppert[15] not only described a definite clinical picture occurring in pachymeningitis, but were the first to call attention to its more frequent occurrence in infancy than had been previously recognized.

Rosenberg,[19] reporting thirty-eight cases, divides the disease into three types:

1. A latent form, in which class of cases there may be seen slight restlessness, no nervous symptoms, enlargement of the head, with separation of the sutures and fontanels.

2. A form with acute nervous symptoms. In these cases, the onset occurs with vomiting. Restlessness, the "hydrocephalic cry" and convulsions follow. The reflexes are exaggerated, and there may be spasm of the extremities.

3. A fulminating form in which the patient is in coma, has frequent convulsions and rigidity of the neck. These are the cases which are usually diagnosed as meningitis. There is usually not much fever.

The enlarged head and separation of sutures, suggesting hydrocephalus, is present in all types.

Retinal hemorrhage is of great diagnostic importance, occurring in one-third of Rosenberg's cases. Optic atrophy is occasionally found; choked disk may be present.

Lumbar puncture usually gives a clear fluid under increased pressure. Occasionally, one may get bloody spinal fluid, which always indicates a tear in the arachnoid.[20] Hemorrhage due to accidental puncture of a vein during lumbar puncture must be excluded. Hemorrhagic fluid obtained on fontanel puncture is of great diagnostic value. This fluid may be truly hemorrhagic, or exhibit a brownish or yellowish coloration due to the presence of old blood. Rosenberg

17. Krücke, L.: Ein fäll von eitrig entzundeter Pachymeningitis hemorrhagica bei Difterie, Inaug. Dissert., Kiel, 1902.

18. Finkelstein, H.: Ueber Pachymeningitis hemorrhagica im Kindesalter, Jahrb. f. Kinderh., 1911, lxxiv, 451; Berl. klin. Wchnschr., 1904, xli, 403.

19. Rosenberg, O.: Ueber Pachymeningitis hemorrhagica im Kindesalter, Berl. klin. Wchnschr., 1911, l, 2272.

20. Quincke, H.: Ueber Lumbalpunction, Deutsche klin., Berlin, 1906, vi, Part 1, p. 351.

found that 80 per cent. of his cases showed the presence of rhinitis, from which the diphtheria bacillus was isolated. He attributes to this rhinitis considerable etiologic importance. The ethmoidal veins which supply the nasal mucous membrane empty into the ophthalmic veins, which empty into the cavernous sinus. Rosenberg thinks there is a possibility of erosions on the nasal mucous membrane causing a sinus thrombosis, which may produce the pachymeningitis. He attempts to explain the case reported by Heubner, which the latter had attributed to congenital syphilis, on similar grounds, believing the coincident rhinitis to be the possible explanation for the presence of pachymeningitis.

Only recently has more attention been called to the possible infectious nature of pachymeningitis in infancy.

Göppert, in 1905, reporting three cases, expressed the opinion that a primary serous subdural exudation occurred in pachymeningitis. He found no similar suggestion in the previous literature on the subject.

Hahn[21] reported a case in which he was able to demonstrate an actual serofibrinous exudate.

In a study of the relationship of pertussis to pachymeningitis, Hada[7] concludes that toxins or bacteria first produce an infection which is subsequently followed by hemorrhages.

The actual occurrence of symptoms of serous meningitis preceding the development of hydrocephalus in a case, which after death showed pachymeningitis, suggests to Freund[22] the possibility of pachymeningitis being of an infectious nature.

Though Rosenberg demonstrated a streptococcus in the bloody fluid obtained from two patients with pachymeningitis, one of whom recovered, and one of whom died with a streptococcus meningitis, he lays no stress on the isolation of the streptococcus in these cases.

Excepting this finding of Rosenberg, in all recent reported cases[23] of pachymeningitis which have included bacterial examinations, no organisms have been demonstrated in the spinal fluid.

Finkelstein[18] concludes that bacteriologic study of this disease has not shown it to be of an infectious nature.

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21. Hahn, H.: Klinischer Beitrag zur lehre von der Pachymeningitis hemorrhagica interna im frühen Kindesalter, Deutsch. med. Wchnschr., 1911, xxxvii, 1518.

22. Freund, W.: Zur Therapie des Hydrocephalus zugleich ein Beitrag zur Kenntnis der Pachymeningitis hemorrhagica im Sauglingsalter, Monatschr. f. Kinderh., 1909, vii, 613.

23. Gordon, A.: Internal Pachymeningitis in Young Children, Jour. Nerv. and Ment. Dis., 1914, xli, 382. Hartje, E.: Zur Casuistik der Meningitis basilaris posterior, Arch. f. Kinderh., 1912, lvii, 333. Schindler, R.: Ein Fäll von Meningocele spuria traumatica kombiniert mit Pachymeningitis hemorrhagica interna, Jahrb. f. Kinderh., 1912, lxxvi, 160.

The diagnosis of the case to be reported was that of pachymeningitis. It is based on the clinical picture entirely.

In this picture there stand out prominently the repeated bloody character of the spinal fluid, the severe retinal hemorrhages, and the fact that the subdural fontanel puncture yielded an amber colored fluid. All of these features have been accepted by Rosenberg and others as indicating the presence of pachymeningitis. Naturally there exists the possibility that we are dealing with a particular case of leptomeningitis, or encephalitis with pronounced hemorrhagic lesions. The lack of a necropsy does not permit the absolute exclusion of such possibilities. If so, then a number of cases reported in the literature as pachymeningitis on purely clinical evidence are subject to the same objections.

Even accepting such possibilities, these cases become important, inasmuch as they may be gradations between the usual form of leptomeningitis and pachymeningitis.

The case herewith reported is one in which the meningococcus was demonstrated in the spinal fluid on several separate examinations.

REPORT OF CASE

History.—Jennie P., Polish girl, born January, 1915, was admitted to The Children's Memorial Hospital, May 10, 1915, on account of convulsions and diarrhea.

Family History.—Parents living and well. No other children. No miscarriages. No known history of tuberculosis in family.

Past History.—Protracted labor, no forceps used. Birth weight 9¼ pounds. No respiratory trouble following delivery. Breast fed one week, following which the infant was fed on various milk mixtures. Feeding intervals irregular. At two weeks she had furunculosis. At four months the patient had three convulsions, cause unknown. Was treated in Out-Patient Department three weeks prior to admission for fracture of left humerus.

Present Illness.—Began May 3, 1915, with convulsions, which recurred frequently for twenty-four hours. Then followed two days, during which time, no convulsions occurred.

May 6, 1915, convulsions recurred, continuing since. Had had a diarrhea; stools described as foul, green, watery. Had had a slight cough; no vomiting.

Physical examination showed an under-nourished baby with no abnormal findings.

During a four-days' stay in the hospital, the temperature was normal, the stools appeared normal, the infant had no convulsions, and gained 9 ounces on a mixture of ⅔ whole milk and ⅓ water, with 3 per cent. additional dextrimaltose.

The case was considered one of convulsions due to improper feeding and the patient was discharged May 14, 1915. May 17, 1915, she was readmitted. The mother stated that the child had a convulsion shortly after returning home and cried much that day and the next. On the second day home the patient vomited and had vomited persistently since. For the previous two days had appeared too weak to cry. Bowel movements normal.

Physical Examination.—Semicomatose. Extremely pale. Does not resist examination. Respirations regular but shallow. Emaciated. Very poor tissue turgor. Corneae dull, eyes fixed.

Head: All sutures of skull widely separated. The anterior fontanel was tense and bulged considerably. Slight craniotabes present. Head appeared large in comparison to body.

Eyes: Pupils equal, left did not react to light. Right pupil reacted sluggishly.

Ears, Nose, Mouth and Throat: Nothing abnormal noted.

Thorax: Rachitic rosary present.

Heart: No abnormality noted.

Lungs: Few mucous râles scattered over chest. No dulness. No abnormal breath sounds.

Abdomen: Level and tympanitic. Liver edge felt 4 cm. below costal margin. Spleen not felt.

Extremities: Slight rigidity.

Laboratory Reports.—White cell count, 20,600.

Hemoglobin (Tallquist), 65 per cent.

Differential Count:

Polynuclears, 76 per cent.; small mononuclears, 14 per cent.; large mononuclears, 6 per cent.; basophils, 4 per cent.

Wassermann: Negative.

Vaginal Smear: No gonococci found.

Urinalysis: Nothing abnormal found.

Throat and Nasal Culture: Negative for diphtheria bacilli.

Von Pirquet reaction negative.

Roentgenogram of head and chest negative.

Lumbar Puncture: Sixty c.c. bloody fluid under increased pressure. Hang-drop shows field full of red blood cells, no organisms seen. Cultures made show growth, within twelve hours, of a large bacillus (contamination).

May 18, 1915. Lumbar puncture: 3 c.c. bloody fluid, no examination made. Left lid drooping. Left foot and hand show occasional twitching.

May 19, 1915. Fronto-occipital circumference, 40.5 cm.

May 20, 1915. Ophthalmoscopic examination (Dr. Alfred Hall): Chorioretinitis with marked hemorrhage throughout both retinae.

May 22, 1915. Lumbar puncture: 5 c.c. bloody fluid under increased pressure. Cultures made in bouillon. After thirty-six hours' growth, diplococcus isolated.

May 25, 1915. General condition somewhat improved. Color better. Responds more to stimuli. Has fairly normal cry during examination. Opens eyes, but apparently does not see. Fontanel tense. Pupils unchanged. Suggestive Kernig's sign on left side. Brudzinsky sign present. Slight spasticity of extremities.

May 27, 1915. Lumbar Puncture: 20 c.c. bloody fluid under increased pressure. Cultures made in human blood agar and plated. After twenty-four hours diplococcus isolated.

May 29, 1915. Lumbar Puncture: 40 c.c. amber colored fluid, under increased pressure. Unstained smears show crenated and degenerated red cells. No organisms; 10 c.c. antimeningitis serum given. Cultures made in bouillon and human blood agar; diplococcus isolated.

May 30, 1915. Patient lies very quietly, but cries when disturbed. Piercing shriek when extremities are manipulated to elicit reflexes. Knee jerks not obtained. No Kernig's sign. Marked spasticity of extremities. Fronto-occipital circumference 42.5 cm. General appearance of hydrocephalus.

May 31, 1915. Lumbar Puncture: Sixty c.c. amber-colored fluid under increased pressure. Cultures made in litmus milk and on plain agar. No growth obtained.

June 2, 1915. Lumbar Puncture: Forty c.c. amber-colored fluid under increased pressure. Smears show many white and red cells and an occasional diplococcus. Cultures made on human blood agar; diplococcus isolated.

June 3, 1915. Ophthalmoscopic Examination (Dr. Alfred Hall): Extreme atrophy of both optic nerves. Hemorrhages of retina clearing up.

June 4, 1915. Lumbar Puncture: Forty c.c. clear yellow fluid under increased pressure. Smears show increased number of leukocytes, polynuclears predominating. No organisms. Cultures on human blood agar; no growth.

June 8, 1915. Lumbar Puncture: Forty c.c. bloody fluid under increased pressure. Cultures in bouillon; diplococcus isolated.

June 11, 1915. Lumbar Puncture: Thirty c.c. clear fluid under increased pressure. Cultures in bouillon; no growth.

June 26, 1915. Lumbar Puncture: Sixty c.c. fluid; first 30 c.c. clear, last 30 c.c. a pale yellow; pressure greatly increased. Cultures in bouillon; no growth. Furunculosis of scalp; furuncles incised; cultures made. Staphylococcus present.

July 13, 1915. Facial expression not as drawn, though there is still marked pallor and universal loss of tissue turgor. Sutures and fontanel are beginning to approximate themselves. Fronto-occipital circumference 41.5 cm.

July 27, 1915. Fontanel bulging somewhat. Lumbar puncture and fontanel puncture done. The fluid obtained at both points was under increased pressure. That from the fontanel (subdural) was amber colored, and on standing showed a deposit of blood. Cultures made in bouillon; no growth. The fluid obtained by lumbar puncture was perfectly clear. Cell count 50. Noguchi: Faint turbidity. Permanganate reduction index, 3.4. Excepting for a short interval when patient had furunculosis, the temperature remained normal throughout illness. Weight practically stationary. Aug. 14, 1915, patient began losing weight, failed steadily, and died August 23. No necropsy granted.

Bacteriology.—The organism isolated from this case of pachymeningitis was demonstrated in cultures of the cerebrospinal fluid obtained from five different lumbar punctures. The organism grew well on human blood agar and in bouillon. Subcultured, it grew on most of the ordinary laboratory culture mediums. On agar slants the growth appeared as slightly larger than pinhead, round, glistening, grayish-white, discrete, elevated colonies, which as growth continued formed a confluent streak with slightly irregular edges.

By Gram staining it appeared as a large gram-negative coccus, occurring in diplo, tetrad or group arrangement, which characteristics it retained in further subcultures.

Several observers[24] have reported the finding of other gram-negative diplococci than the meningococcus in the cerebrospinal fluid. Furthermore, the importance recently ascribed to the parameningococcus[24] as a causative agent in resistant cases of epidemic meningitis, made it necessary to determine by differential tests the exact nature of the organism isolated.

It has been shown by von Lingelsheim[25] that the meningococcus can be differentiated from other gram-negative diplococci by its reactions to various sugars. According to his work, the meningococcus changes dextrose and maltose, but not levulose, saccharose, galactose and lactose.

The medium used for the differentiation was prepared in the usual manner.[26]

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24. Kutscher: Kolle-Wassermann Handbuch d. path. Mikro-organismen, Jena, 1912, p. 589. Dopter, M.: Diagnostic bactériologique des méningites cérébrospinales à méningocoques et à parameningocoques; Societie med. d. Hôpitaux d. Paris, Series 3, 1914, xxxvii, 1217.

25. v. Lingelsheim, W.: Klin. Jahrb., 1906, xv, 373.

26. Kolle-Hetsch: Die Experimentelle Bakteriologie und du Infektionskrankheiten, Berlin, 1911, p. 378.

The growth on this medium was slow in appearing, no culture showing growth before forty-eight hours, while some showed no growth before sixty hours. The colonies on the dextrose and maltose ascites agar soon turned pink, while those in the other sugars remained colorless or slightly blue colonies.

Albrecht and Gohn[27] were the first to note the occurrence of specific agglutinins in the blood serum of animals receiving repeated injections of meningococci.

Specific agglutinins in the serum of patients ill or convalescent from epidemic meningitis were first noted by Bettencourt and Franca.[28]

Following the work of Dopter and others on the parameningococcus, agglutination through specific serum reactions is now considered the most trustworthy guide in the identification of the meningococcus.[29]

While normal serums may agglutinate the meningococcus in dilutions of 1 to 20, serums containing specific agglutinins will agglutinate the meningococcus in greater dilutions.[28]

The serums used in the present instance were as follows:

1. Jennie: Patient's own serum.
2. Stephanie: Serum of a convalescent epidemic meningitis patient who had responded to treatment with Flexner's serum.
3. Antimeningitis serum: New York State Board of Health.
4. Normal serum (author's blood).

A suspension of the organism having been made in 0.9 per cent. salt solution, various dilutions of the serum were then made to which were added the same amount of suspension. The tubes were placed in the incubator at 37 C. for two hours, then transferred to the ice chest for twenty-four hours.

The accompanying table gives the results of the agglutination determinations:

RESULTS OF AGGLUTINATION DETERMINATIONS

	1 to 40	1 to 60	1 to 80	1 to 100	1 to 120	1 to 160	1 to 320	1 to 640
Jennie s serum	+	+	−	−	±	−	−	−
Stephanie s serum	++	++	+	−	−	−	−	−
Antimeningitis serum	+	+	±	−	−	−	−	−
Normal serum	−	−	−	−	−	−	−	−

27. Albrecht, H., and Ghon, A.: Ueber die Aetiologie und path. Anatomie der Meningitis cerebrospinalis epidemica, Wien. klin. Wchnschr., 1901, xiv, 984.

28. Bettencourt, A., and Franca, C.: Ueber die Meningitis cerebrospinalis epidemica und ihren Erreger, Ztschr. f. Hyg. u. Infectionskr., 1904, xlvi, 463.

29. Flexner, Kraus and Levaditi: Handb. d. Tecknik, u. Methodik d. Immunitatsforsch., Jena, 1914. Quoted by Wollstein, M.: Jour. Exper. Med., 1914, xx, 201.

DISCUSSION

It appears probable that pachymeningitis hemorrhagica as it occurs in infancy is an infectious disease, which may be caused by the meningococcus or other organisms. That this possibility should have passed unnoted by students of pachymeningitis seems all the more remarkable when it is recalled that Weichselbaum[30] in his early work with the meningococcus was able to produce pachymeningitis and leptomeningitis and acute encephalitis by the injection of this organism.

His experiments were done on dogs, the injection of the meningococcus being made subdurally after trephining the skull. The dogs appeared well for several hours. After five or six hours they appeared sick. One dog died the same evening. The second, acutely ill, was killed on the third day. The third dog died on the twelfth day. The first two dogs showed fluid blood between the dura and the cerebrum, a hemorrhagic area of softening in the cerebrum, with much injection of the meninges. The third dog showed a thick reddish exudate between the dura and the brain, while in the brain substance there was an abscess the size of a hazelnut, and numerous hemorrhages.

It seems probable that pachymeningitis and leptomeningitis are but different manifestations of a single process, the meningococcus being the offending organism in both diseases.

In the light of Rosenow's[31] work with the streptococcus, it seems possible that the meningococcus, in like manner, at one time may produce leptomeningitis, at another pachymeningitis. That transition forms of meningitis do occur, suggesting such a possibility, is evident from the studies of various epidemics of the disease. While the predominating feature of the usual case is an acute fibrinopurulent exudate involving the pia-arachnoid of the brain and cord, the dura is usually vascular,[32] and hemorrhages in the brain and other organs are common. The extent of these hemorrhages varies considerably in various epidemics. Thus Bettencourt and Franca[28] in their studies on epidemic meningitis comment on the frequency of hemorrhages in their series, the histologic picture of the brain being often that of meningoencephalitis hemorrhagica. Subarachnoidal hemorrhages are also noted by these observers.

As there are various forms of meningitis, produced by various organisms, it is quite probable that similar divisions occur among the

30. Weichselbaum, A.: Ueber die Aetiologie des akuten Meningitis cerebrospinalis, Fortschr. d. Med., 1887, v, 620.

31. Rosenow, E. C.: Jour. Infec. Dis., 1915, xvi, 240; ibid., xvi, 367; ibid., xvii, 219.

32. Westenhoeffer, M.: Pathologisch-anatomischen Ergebnisse der Oberschlesischen Genick-starre epidemie von 1905, Klinisches Jahrb., 1906, xv, 657.

cases of pachymeningitis. Indeed, the cases reported by Rosenberg of pachymeningitis in which streptococci were isolated, and the case reported by Dupérié[33] in which tuberculous meningitis and pachymeningitis were present in the same case, confirm this idea. That organisms have not been isolated in these cases heretofore is probably due as much to the lack of search, as to the difficulty often encountered in their isolation.

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33. Dupérié, R., and Dubourg, E.: Pachyméningite hémorrhagique. Hémorrhagie méningée et tuberculose encéphalo-méningée chez un enfant de deaux ans, Gaz. hebd. d. sc. méd. de Bordeaux, 1913, xxxiv, 157.

PARAPNEUMONIC EMPYEMA *

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The term *"pleuresie parapneumonique"* was first proposed by Lemoine[1] in 1893, to describe the occurrence of fluid in the pleural cavity coincident with pneumonia. He pointed out the fact that the occurrence of fluid in the chest during the early part of an attack of pneumonia is more frequent than is generally supposed, occurring in possibly five to six per cent. (Grisale, 12.6 per cent.; Deustl, 16 per cent.; Fismer, 15 per cent.; Magnus Hus, and Jugenser, 4 or 5 per cent.). He further states that the fluid of parapneumonic pleurisy is always serous, while that of metapneumonic pleurisy, that following the crisis, is always purulent.

Le Damnay[2] in a thesis on pleurisies, in 1897, also calls attention to the occurrence of fluid in the thoracic cavity coincident with pneumonia, and gives histories of four such cases. Since these researches a large number of cases of parapneumonic pleurisy has been reported.

For his thesis in 1901 Siems[3] collected twenty-six cases. All patients were adults. The amounts of fluid obtained varied from a few drops to 700 c.c. In two cases no puncture was made. From his data Table 1 is made with regard to the character of the fluid and the bacteriologic findings.

TABLE 1.—CHARACTER OF FLUID AND BACTERIOLOGIC FINDINGS

Type of Fluid		Micro-Organisms Present (Smears, Cultures, or Animal Inoculation)
Serous	8	4
Serofibrinous	11	2
Blood stained	1	0
Seropurulent	2	1
Purulent	2	1

In four of these cases the fluid obtained from the pleural cavity was purulent or seropurulent. They were as follows:

1. A patient 39 years of age with pneumonia. Puncture gave "5 c.c. of a liquid seropurulent, cloudy, very rich in pus cells." No micro-organisms in

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1. Lemoine: Semaine méd., 1893, p. 12.

2. LeDamnay: Recherches sur les pleuresies sero-fibrineuse primatives et secondaries, Thèse, Paris, 1897.

3. Siems: Les Pleuresies Contemparaines de la pneumonie, Thèse, Paris, 1901.

smears or cultures. Inoculation into a mouse gave no result. The patient recovered, the fluid being absorbed.

2. Two days before death puncture gave 100 grams of "seropurulent fluid" containing many pneumococci. Inoculation of mice caused death, the pneumococci being recovered from their blood. At necropsy the patient showed gray hepatization of the right lung and a fibrinopurulent pleurisy.

3. A laborer four hours after a blow on the side was brought into the hospital with hemoptysis. Pneumonia started four days later and puncture gave 10 c.c. of sterile "pus." On the sixth day 10 c.c. of "purulent fluid," also sterile, was obtained. There was spontaneous absorption and uneventful recovery.

4. Patient aged 45 years. Puncture gave a few drops of "yellow fluid" from which a pure culture of pneumococci was obtained. Inoculation of mouse caused death in twenty-four hours. The patient died on the seventh day of his pneumonia. At autopsy "purulent fluid" was found encapsulated by fresh adhesions between the lung and mediastinum. Virulent pneumococci were found in this fluid also.

Widal and Gougerot,[4] in 1906, describe two cases, comparing the fluid to that found in the cerebrospinal canal after certain syphilitic affections. They call especial attention to the presence in the fluid of large numbers of polymorphonuclear leukocytes which retain their morphologic and functional integrity, and the complete absence of any micro-organisms, as shown by smears, cultures and animal inoculation. They say also that these fluids resemble closely those resulting from the injection of sterile bouillon into the peritoneal cavity of guinea-pigs.

Their patients were 24 and 34 years of age, both having typical lobar pneumonia.

1. On the fourth day of the disease 5 c.c. of fluid was obtained by puncture. Two days later none could be obtained.

2. On the fourteenth day while the disease was still actively present 100 c.c. of fluid was obtained. Four days later only a few drops of "blood-stained fluid" could be removed. The fluids of both cases were sterile but opaque, containing many polynuclear cells.

Pende,[5] in 1909, describes three cases, ages 13, 14 and 15 years, in which "purulent" fluid was obtained by puncture. These contained no organisms but many polymorphonuclear cells. They were absorbed spontaneously, one in three and the other two in four days.

Neuman,[6] in 1912, reviews the literature and reports two cases which are later included in those reported by Gerhardt.[7] He lays special stress on the fact that parapneumonic fluids are usually sterile.

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4. Widal and Gougerot: Bull. et mém. Soc. d. hôp. de Paris, 1906, vii.
5. Pende: Policlinico, Rome, 1909; ref. Zentralbl. f. inn. Med., 1910, p. 513.
6. Neuman, K.: Parapneumonic Empyema, Inaugeral Dissertation, Wurzburg, 1912.
7. Gerhardt: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, xxvi.

Dumont,[8] in 1912, observed three cases.

1. A patient 26 years old had active signs of pneumonia. Punctures on the first and third days gave only blood. On the fourth day by puncture 20 c.c. of opaque "pus" was removed, which on centrifugalization gave a sediment and an opalescent supernatant fluid. The cells were 70 percent polymorphonuclear leukocytes. No organism could be found by cultures and inoculations gave no results.

2. A patient 52 years old. On the fifth day of pneumonia "some pus" was removed by puncture. On the eighth day "more pus" was removed. On the fourteenth day the Roentgen ray showed a shadow and on puncture "serofibrinous fluid" was obtained. On the thirty-second day there was evacuated completely 40 c.c. The fluid contained no micro-organisms.

3. A patient 24 years old. Puncture on the tenth day gave 20 c.c. of "purulent fluid," 70 per cent. polymorphonuclear cells. No micro-organisms by smears, cultures or inoculation. No fluid was found the following day.

Gerhardt,[7] in 1913, reports five cases.

1. A patient 46 years old. Puncture on the second day of pneumonia gave 1 c.c. of "sterile pus."

2. A patient 14 years old. Puncture on the first day of pneumonia gave 1 c.c. of "pus."

3. Patient 18 years old. Puncture on the day before crisis, the seventeenth day, gave a "purulent exudate."

4. Patient 28 years old. On the fourth and sixth days puncture gave a "purulent exudate."

In all four cases the fluids were sterile by smears, cultures and inoculation.

5. Patient 15 years old. Puncture on the fourth day gave "pus" containing gram-positive, encapsulated, diplococci, which by inoculation were shown to be of very low virulence. All five cases recovered with spontaneous absorption.

Vaughan, Jr.,[9] says that "Maragliano demonstrated serofibrinous or fibrinopurulent exudate in 65.5 per cent. of cases of typical pneumonia, by puncture. Marin found 41.5 per cent. of 978 cases at autopsy to have pleural fluid, and Kerr found in 178 autopsies 69 per cent. with fluids, 74 fibrinous, 38 serofibrinous and 6 acute purulent."

Levy[10] mentions cases with fluid from the pleural cavities in pneumonia, bronchopneumonia and influenza, in which ten were serous and nine "purulent." Three of the serous fluids were free from organisms; the others all contained organisms. Unfortunately his data are very scanty.

Sauer,[11] in 1914, observed two cases in children, the only cases reported in children.

1. Four years old. The patient had pneumonia involving the lower and middle right lobes. Puncture two days before crisis gave a few drops of "pus" which contained gram-positive diplococci. The next day 7 c.c. of similar "creamy pus" was withdrawn. Gram-positive, encapsulated diplococci were shown by

8. Dumont and Mossy: Bull. et mém. Soc. d. hôp. de Paris, June 14, 1912; ref. Semaine méd., 1912, p. 299.

9. Vaughan, Jr.: Jour. Michigan State Med. Soc., 1914, xiii, 573.

10. Levy, E.: Arch. f. exper. Path. u. Pharmakol., 1890, xxvii, 369.

11. Sauer: Arch. Pediat., March, 1915, xxxii.

smears and cultures. By puncture six days after crisis no fluid was obtained. The patient recovered, the fluid being spontaneously absorbed.

2. Patient 3 years old. Puncture was made on the fifth day and 0.5 c.c. of "pus" aspirated. It contained leukocytes but no organisms. Cultures were sterile. On the following day there could be heard on deep inspiration, a friction rub. The patient recovered.

AUTHOR'S CASES

In a series of fifteen cases of typical lobarpneumonia or bronchopneumonia, in children under 4 years of age, seen in The Children's Memorial Hospital during January, February and March, exploratory punctures of the chest were made as early as possible in the course of the disease. The needle was put in over the area of greatest impairment as shown by physical signs and roentgenograms. In only one of the cases where fluid was not found at the first puncture, were subsequent trials made, and no fluid was found until the twenty-second day, when a typical metapneumonic empyema was found.

In six of these fifteen cases (40 per cent.) fluid was recovered by puncture before the seventh day of the disease, always before the crisis. Five of the six fluids were opaque and yielded a large clot. They contained a large number of cells, between 70 and 80 per cent. polymorphonuclear leukocytes. No micro-organisms could be demonstrated in them by smears. Cultures on agar, milk, bouillon, and with some on blood-agar, gave no growths. Inoculations into mice were without harmful results, except in one case in which the mouse died within twenty-four hours, but no lesions were found and no organisms could be grown from its heart's blood or serous cavities. In all five cases the fluids were absorbed spontaneously, as was shown by later punctures and roentgenograms. The clinical course of the disease was never noticeably affected by the presence of these fluids.

In one case two days after fluid had been found the patient died from other causes than the pneumonia. The autopsy showed no fluid in the pleural cavity. There were several large areas of bronchopneumonia. Over one of these areas, in about the region where puncture had been made and fluid obtained, the pleural surface was somewhat dulled and showed a thin, very fresh, slight deposit of fibrin.

In the sixth case, on the second day of the disease, about 5 c.c. of purulent fluid was removed by puncture. It was opaque, did not coagulate, but on standing separated into a heavy sediment and a semiopalescent supernatant fluid. It contained many polymorphonuclear cells and also cocci in diplo- and double-chain form. On all ordinary mediums cultures grew well. Inoculation of 1 c.c. into the peritoneal cavity of a mouse caused death in less than twenty-four hours, the organism being recovered from its blood and serous cavities. The group of pneumococci to which this organism belonged was not determined.

The patient was operated on and the pleural cavity freely drained, but death occurred in a few days. No necropsy was obtained.

In brief the histories of these cases follow:

CASE 1.—Peter O., aged 6 months, was admitted to the hospital January 1. His mother was at that time in a hospital with pneumonia. Birth and previous history negative. Breast fed until the onset of mother's illness.

Present Illness.—For two weeks preceding admission there was coughing, restlessness and loss of appetite, slight diarrhea and loss of weight.

Examination.—On admission examination showed a well nourished, well developed, rachitic baby boy. Occasional cough. Chest symmetrical, expansion good, respiration neither rapid nor labored. Percussion note of normal relative intensity over entire chest. There was no tubular breathing anywhere, but a few moist râles in the interscapular region. Otherwise negative.

On the third day in the hospital, January 3, cough continued. Respirations somewhat increased in rate. Lungs: Anteriorly no dulness, no râles, no bronchial breathing. Over the left lower back percussion note slightly high pitched, many medium moist râles and a few large dry râles. Occasional râles over the right back. White blood cells 26,000.

Roentgenogram of Chest: A rather broad mediastinal shadow and rather profuse, though not intense mottling throughout both lungs — about the same on both sides.

Von Pirquet test negative.

January 6, marked dulness at the left base with distant tubular breathing. A needle was put into the left pleural cavity in the sixth interspace and 5 c.c. of fluid drawn off. This fluid was thin, cloudy and coagulated. Smears showed large numbers of leukocytes, but no organisms. Cultures gave no growth.

January 7. Roentgen ray showed a shadow at the left base.

January 8. Dulness still present at the left base with distinct tubular breathing. A needle was put into the pleural cavity near the point of previous puncture. Only a few drops of fluid could be obtained. Sterile as previously.

January 11. Dulness as before. Roentgen-ray shadow at left base of same density as on former exposure.

January 15. Dulness less marked. No more tubular breathing. Crisp crepitant râles.

January 23. Roentgen examination: Chest clear. Other signs returning to normal. From this time on the chest remained normal.

CASE 2.—Harriet J., aged 6 months, admitted to the hospital in October, 1914, with bronchitis and nutritional disturbances. Family history unimportant.

Previous History.—Birth normal. Had never been strong. Always had gastro-intestinal disturbances, and one convulsion.

Examination.—Showed a poorly nourished baby girl. Dec. 25, 1914, the lungs were clear.

Jan. 12, 1915. Patient had been coughing for several days. Throat rather red. Chest: no dulness on percussion, no tubular breathing, but diffuse coarse, moist râles.

January 13. High pitched moist râles over left back.

January 18. Over the left base quite marked impairment of the percussion note. Breath sounds over this area faintly tubular. Many râles throughout both lungs.

A needle was put into the pleural cavity in the seventh interspace at the angle of the scapula and about 1 c.c. of thin cloudy fluid, which coagulated, was obtained. Smears showed many pus cells; no micro-organisms. Cultures gave no growth. Injection of 0.75 c.c. into the peritoneal cavity of a mouse caused no appreciable result.

January 19. Marked dulness at the left base and distinctly tubular breath sounds.

January 20. Patient died. Immediately after death a needle was put in the chest at about the point of first puncture, but only a few drops of fluid were obtained. This was found sterile by smears and cultures.

Note at Necropsy (Dr. Riley).—On opening the chest there was no free fluid in the pleural cavities and no adhesions. Over the left lower lobe was a slight, sticky, thin fluid. The left lung showed nodules of bronchopneumonia in posterior portion of upper lobe and much consolidation of the paravertebral portion of lower lobe. Over this region the pleural surface was slightly dulled by a thin fibrinous exudate.

CASE 3.—Harold Mc., aged 4 years, admitted to the hospital Jan. 22, 1915. Family history unimportant. Previous history negative.

Present Illness.—This began five days before admission, with cough, fever and vomiting.

Examination.—On admission examination showed a well developed, well nourished child. Respirations rapid with expiratory grunt. On percussion there was marked dulness from the third left interspace in the axilla to the base of the lung posteriorly and anteriorly. Over this area were crepitant and subcrepitant râles and bronchial breathing. Remainder of the lungs normal. White blood cells 34,000. Polymorphonuclears 92 per cent.

January 23.—Roentgen examination of chest showed uniform dulness at the left base below the seventh space.

January 24.—Dulness over left back with distant tubular breathing. A needle was put into the thoracic cavity in the ninth interspace below the angle of the scapula and 5 c.c. of greenish-yellow, viscid fluid obtained. It coagulated quickly after removal. Polymorphonuclears 66 per cent. No organisms in smears: cultures gave no growth; 1 c.c. injected into a mouse gave no results.

January 25. Area still dull. Bronchial breathing has disappeared. White blood cells 27,000.

January 27. By puncture 0.5 c.c. of bloody fluid was obtained. It was sterile.

January 29. Impairment less marked. Many râles, but no tubular breathing. Roentgen-ray examination of chest showed shadow over entire lower left.

January 30.—Temperature now continually normal.

February 2.—Patient has entirely recovered. Dulness has disappeared.

CASE 4.—Edwin Z., aged 17 months. Admitted to hospital January 31. Family and previous history not remarkable.

Present Illness.—This began one week before admission, with diarrhea, cough, fever, loss of appetite and vomiting.

Examination.—This showed a well-nourished boy, coughing much. Chest symmetrical; respirations accelerated but not labored. Dulness on percussion over the right back and axilla. Fine high-pitched râles, tubular, diminished breath sounds. Remainder of lungs normal. White blood cells 16,000.

February 2. Puncture made at two points below the right scapular; 1.5 c.c. of bloody, serous fluid, which coagulated, was obtained. Smears showed no organisms. Cultures remained sterile. One c.c. injected into the peritoneal cavity of a mouse was followed by death in twenty-four hours. No lesion of organs. No cultures obtainable from blood or serous cavities.

February 3.—Roentgen-ray examination of chest showed slight dulness at the right base below the angle of the scapula.

February 7. Puncture made but no fluid could be obtained.

February 12. Patient in good condition, left the hospital.

CASE 5.—Thomas M., aged 9 months, admitted to hospital March 31. Family history unimportant. Previous health good until last two months.

Present Illness.—This started six weeks before admission with fever, cough, vomiting and diarrhea.

TABLE 2.—PNEUMONIA CASES WITH PLEURAL FLUID

No.	Name	Age Months	Clinical Diagnosis	Admitted	Date of Exploratory Puncture	Probable Day of Disease of Puncture	Amount c.c.	Type of Fluid	Cultures	Animal Inoculation
1	Peter O.	6	Lobar pneumonia, enteritis, otitis media	1/ 1/15	1. 1/ 6/15 2. 1/ 8/15	Fourth Sixth	5 1	Turbid; slightly coagulating; containing many pus cells; no bacteria.	No growth on agar, milk, or bouillon.	.....
2	Harriet J.	6	Bronchitis, broncho-pneumonia, enteritis	11/27/14	1. 1/18/15 2. 1/20/15	Sixth Eighth (post-mortem)	1 †	Thin, cloudy, coagulating; many pus cells; no bacteria.	No growth on ordinary mediums.	0.75 c.c. into peritoneal cavity of a mouse; no developments.
3	Harold McM.	48	Lobar pneumonia	1/22/15	1. 1/24/15 2. 1/27/15	Sixth Ninth	5 0.5	Green, yellow, viscid, coagulating; many cells; 62 per cent. P. M. N.; no bacteria.	No growths	1 c.c. into peritoneal cavity of a mouse; no developments.
4	Edwin Z.	17	Lobar pneumonia	1/31/15	1. 2/ 2/15 2. 2/ 7/15	Fourth Ninth	1.5 0	Blood stained serous fluid, coagulating; no bacteria.	No growth	1 c.c. into peritoneal cavity of mouse; death in 24 hours; no lesions; no bacteria from heart's blood or peritoneum.
5	Thomas N.	9	Lobar pneumonia, empyema	3/31/15	1. 3/31/15 2. 4/ 1/15 3. 4/ 2/15 4. 4/ 5/15 5. 4/ 6/15*	Fourth Fifth Sixth Ninth Tenth	3 2 0 2 0	Thin cloudy, coagulating; many pus cells; no bacteria; (4) bloody.	No growth on agar, blood agar, milk, broth	.....
6	Lena B.	9	Broncho-pneumonia, empyema	3/ 9/15	1. 3/11/15 2. 3/12/15 3. 3/13/15 Operation	Fourth Fifth Sixth	5 ‡	Thin pus; creamy pus; not coagulating; cocci in diplo- and chain form.	Profuse growth on agar and in milk and bouillon	1 c.c. into peritoneal cavity of mouse; death in 20 hours; cocci recovered from heart's blood and serous cavities.

* Alboline injected. † Few drops. ‡ Very much.

TABLE 3.—Pneumonia Cases Without Pleural Fluid

No.	Name	Age Years	Clinical Diagnosis	Date Admitted	Date of Exploratory Puncture	Probable Day of Disease of Puncture	Amount c.c.	Character of Fluid	Cultures
7	Maurice C.	5/6	Lobar pneumonia; empyema	1/13/15	1. 1/18/15	7	*	Blood stained	No growth
					2. 1/24/15	13	0	.....	.....
					3. 2/ 2/15	22	30	Creamy pus	Streptococci
					4. 2/ 4/15	24	5	Creamy pus	Streptococci
					5. Operation	25	++	Creamy pus	Streptococci
8	Eleanor F.	2	Lobar pneumonia	1/15/15	1/17/15	..	†	Blood stained; no organisms	No growth
9	Marie O.	3	Lobar pneumonia	2/ 6/15	2/ 7/15	7	0	.....	.....
10	Chessie R.	1⅔	Bronchopneumonia	2/25/15	2/26/15	4	†	Blood stained; no organisms	No growth
11	Dorothy F.	2	Lobar pneumonia	2/ 6/15	2/12/15	..	0	.....	.....
12	Herman G.	2½	Bronchopneumonia	2/24/15	2/26/15	5	0	.....	.....
13	Kosta P.	2	Lobar pneumonia	3/16/15	3/17/15	5 (?)	0	.....	.....
14	John O.	3	Bronchopneumonia	3/16/15	3/19/15	6	0	.....	.....
15	Helen C.	6	Lobar pneumonia	3/23/15	3/27/15	6	0	.....	.....

* Few drops. † Less than 1 c.c.

TABLE 4.—Summary of Cases by Various Authors

Collected by	No. Cases	Type of Fluid	Amount of Fluid c.c.	Cultures	Results	Ages
Siems	26	Serous 9 Sero-fibrinous 11 Purulent 4	A few drops to 700	Sterile, 14; pneumococci, 8	Recovered, 18; Died, 8	All adults
Widal	2	Seropurulent (?)	5 and 100	Sterile	Recovered	24 years 34 years
Pende	3	Purulent fluid	.....	Sterile	Recovered	13 years 14 years 15 years
Dumont	3	"Pus" 2 (?)	20 to 40	Sterile	Recovered	26 years 52 years 24 years
Gerhardt	5	Pus and purulent fluid (?)	0.5 to 5	4 sterile; 1 pneumococci	Recovered	26 years 14 years 18 years 28 years 15 years
Sauer	2	Pus (?) Pus	1	1 sterile; 1 pneumococci	Recovered	4 years 3 years
Gerdine	6	Serous or seropurulent Pus 1	1 to 5	5 sterile; 1 pneumococci	Recovered, 4; Died, 2*	6 months 6 months 9 months 9 months 17 months 4 years

* Death due to other complications in one case.

Examination.—On admission examination showed a well nourished, well developed baby, very ill. Respiration rapid. Dulness, suppressed breath sounds and many medium, moist râles over lower left back.

March 31. A puncture was made over the lower left lobe and about 3 c.c. of thin turbid coagulating fluid was obtained. Smears showed no organisms. Cultures gave no growth. Animal inoculation with no results.

April 1. Puncture over left base 2 c.c. of thin blood-stained sterile pus obtained.

April 4. Dulness less over left base. Breath sounds clearer. No fluid obtained by puncture.

April 5. Dulness more marked. Puncture gave 2 c.c. of very bloody fluid. Sterile as before. April 6. Puncture. No fluid could be found. The patient recovered.

Case 6.—Lena B., aged 9 months, admitted March 9, 1915. Family history and previous history unimportant.

Present Illness.—This started the day before admission, with vomiting.

Examination.—On admission examination showed a well nourished, well developed baby. Chest dulness over left side and lower lobe in back. Bronchial,

distant breath sounds over area of impairment. Moist râles over entire side. Right lung normal. White blood cells 14,900.

March 11. Puncture made at angle of left scapula and 5 c.c. of true pus separating into layers without coagulation, were removed. Smears showed leukocytes, endothelial cells and cocci in groups, double chains and pairs. Cells 40,000 per c.mm. Cultures showed rapid growths.

Roentgen-ray examination of chest showed on the entire left side a uniform shadow.

March 12. Dulness over left side more marked.

Puncture made; 6.5 c.c. fluid removed. It was exactly as that of the previous day. One c.c. injected into the peritoneal cavity of a mouse was followed by death in less than twenty hours. Cultures from the heart's blood and serous cavities of the mouse showed the same organism in pure culture as obtained from the pus from the baby's chest.

Roentgenogram showed shadow of entire chest on left side.

March 13. The chest opened and pus evacuated at operation (Dr. Buford). Pus continued to discharge through drainage tube during next four days.

March 17. Patient died. No necropsy obtainable.

Tables 2 and 3 summarize the findings in my series of cases.

Table 4 shows the findings in all cases reported, including my group.

Table 5 shows the grouping according to the nature of the fluids and the bacteriologic findings.

TABLE 5.—GROUPING ACCORDING TO NATURE OF FLUID AND BACTERIOLOGIC FINDINGS

Total number of cases collected	47	Cultures made in	42
Definitely serous or serofibrinous	28	Pneumococci (Death in 3)	4
		Sterile	22
Definitely purulent or seropurulent	4	Pneumococci	3
		Sterile	1
Without sufficient description indefinitely "purulent"	13	Pneumococci	3
		Sterile	10
No puncture (physical signs)	2		

In many of the cases reported the description of the fluids obtained are not sufficient to determine their exact nature. They are called "seropurulent," "purulent fluids," "purulent exudate," and "pus," or are mentioned as "cloudy," "opaque" or "rich in pus globules," while others are "cloudy fluids which are apparently seropurulent." Many times the fluids are said to be "very rich in fibrin." It would seem that these fluids are probably similar to some of ours, which, though cloudy and containing many pus cells, were not true pus, since there was definite coagulation. In some instances fibrin deposits took place in the pleural cavity, as was shown by one case at necropsy (this series), and suggested in another case (Sauer) by the presence of a friction rub on the day after fluid had been found. In some cases, however, there was no coagulation, the fluid dividing into a cellular sediment and liquid serum.

For the formation of pus two conditions are necessary according to Opie;[12] the accumulation of leukocytes and the necrosis and liquefication of cells and tissue elements. Pus consists of: (1) the constituents of the exuded blood plasma; (2) the constituents of leukocytes and tissue cells that exist free in the pus; (3) the products of digestion of the proteins of the leukocytes and necrosed tissues. It divides into two chief parts, pus corpuscles and pus serum. This pus serum differs from blood serum chiefly in the substances added to it through the proteolytic changes that occur in pus, and also in that it has lost its antiproteolytic property, containing instead free leukoprotease. The fibrinogen that escapes from the vessels into suppurating areas becomes so altered that pus will not coagulate even on the addition of fibrin ferment.

In the majority of cases where the fluids were serofibrinous, they were free from bacteria in smears, by cultures and by animal inoculation (for instance, in 14 of 20 cases from Siems). In the cases in which the description permits us to speak of truly purulent exudate (four in all) micro-organisms were found in three. There remain a number of cases (thirteen) in ten of which the fluids designated as seropurulent or purulent were found sterile. The descriptions of these fluids are not sufficiently detailed to determine whether they were real pus or not. It is probable that in some of these cases an actual purulent exudate was present in spite of the negative bacteriologic findings. From the available data it would seem where we are dealing with frankly purulent fluids, micro-organisms are likely to be present. This is in contradiction to the statement made by Gerhardt, for instance, who, like others, seems to regard the absence of micro-organisms more or less characteristic of the "parapneumonic empyema." The frequency or rarity with which micro-organisms are present in such empyema can not be decided at present, but we have sufficient data to warrant the statement that the absence of bacteria certainly cannot be regarded as characteristic of this complication of pneumonia. It is reasonable to suppose that the fluids will show a gradual transition from serous to purulent. If no organisms are present in the pleural cavity, the fluid may remain serous or serofibrinous with few or many leukocytes, whereas the presence of organisms may lead to the formation of pus. So when a purulent exudate is found, it is probable that in the majority of these cases organisms have been present at one time or another.

The organisms were not always of a high grade of virulence, as shown by animal inoculation. This difference in virulence of the

12. Opie, Inflammation, Arch. Int. Med., 1910, v, 541; and Jour. Exper. Med., 1903, ix.

organisms may be of use in prognosis. A possibility of error must be kept in mind. The introduction of this foreign fluid into the peritoneal cavity may kill the mouse, as in one of our cases. The mouse died in twenty-four hours, but no lesions were found and no organisms could be grown from the heart's blood or serous cavities. In the cases where death of the mouse occurred in a short period and with inoculation of small amounts of fluid, the patient also died; while when the animal survived, the patient recovered and the fluid was absorbed spontaneously. It is evident, therefore, that the cases in which a real parapneumonic empyema occurs need not all be of a benign type as Gerhardt claims.

This is of further importance in its bearing on the treatment of these cases. Since the serous fluids and the purulent ones in which the organisms are of low grade virulence are, as a rule, spontaneously absorbed, surgical interference is not needed unless the amount is so large as to cause discomfort. On the contrary, where organisms of high grade virulence are found, surgical treatment may perhaps enter into consideration.

Although the literature on this subject seems large, we feel that the actual number of cases with sufficient description of the fluid found is too small for very definite deductions. However, we may put forward tentatively the following conclusions:

CONCLUSIONS

1. Fluid is present in the pleural cavity in a large number of cases of pneumonia before the crisis and can be demonstrated, sometimes by physical signs, sometimes by Roentgen ray, and by puncture, even when other physical signs are not apparent.

2. The clinical course of the pneumonia may not be altered by this complication.

3. In the majority of cases the fluid is serofibrinous in character, though perhaps containing a large cellular element, polymorphonuclear in type. These fluids are sterile as a rule.

4. True pus is present much more rarely and may contain organisms of more or less virulence. The frequency of the presence of organisms in these cases cannot be decided on the data as yet secured.

5. The virulence of the isolated organisms determined by animal inoculation seems to be of value in prognosis.

6. Only in cases with serofibrinous and purulent fluids containing organisms of a high grade of virulence should surgical interference enter into consideration.

THE NUTRITIVE VALUE OF BOILED MILK*

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The experimental work involved in this report is the result of an attempt to determine the comparative nutritive efficiency of milk heated to different temperatures. There is considerable evidence in the literature to the effect that scurvy among infants may be caused by feeding cooked milk exclusively; in fact, this notion is so prevalent that many pediatrists still insist on giving raw cow's milk, notwithstanding that the hygienic conditions of this may be far from desirable. It is only in our larger cities that certified milk may be obtained, and even here the price makes it prohibitive for the great majority of homes.

In order to meet present conditions and to make milk more nearly safe for infant feeding, the practice of pasteurizing or boiling has been resorted to. Pediatrists differ as to the relative value of these two processes. The European pediatrists[1] report excellent results with boiled milk—the time of boiling varying within comparatively wide limits. The American pediatrists, on the other hand, have favored the pasteurization process. However, the fact that casein curds sometimes found in the stools of infants fed either raw or pasteurized cow's milk are almost unknown in the European clinics, leads us to believe that boiled cow's milk may be better digested by infants than raw or pasteurized. This assumption is further borne out by the work of Brenneman,[2] who has shown that the clot formed from boiled cow's milk during gastric digestion more nearly resembles the clot formed during the digestion of woman's milk. It is much finer than that formed from raw milk, thus making for more complete digestion and absorption further on in the digestive tract. But conclusive experimental evidence as to the relative nutritive value of raw and cooked milk is lacking, owing to the fact that the experiments with animals have been continued for too short a time, and in the case of

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* From the Department of Home Economics, University of Wisconsin.

1. The literature has been reviewed by Lane-Claypon. Report to the Local Government Board, London. New Series, 1912, No. 63.

2. Brenneman, J.: Jour. Am. Med. Assn., 1913, lx, 575.

babies, other substances, such as cereal waters, or various fruit juices have been superimposed on the basal diet. Furthermore, in many cases, the records leave one in doubt as to just what is meant by boiling. It is conceivable that milk brought just to the temperature of 100 C. is less changed chemically than that sustained at this temperature for a considerable period. The importance of knowing more definitely regarding the nutritive efficiency of pasteurized milk and milk boiled for different lengths of time, is obvious.

PLAN OF INVESTIGATION

In our investigation, rats just past the suckling period were fed milk boiled one minute, five minutes, and forty-five minutes, respectively. Other rats were fed pasteurized milk[3] and one group was given milk heated in an autoclave to a temperature of 114 C. for forty-five minutes. Rats on raw milk were used as controls. In each case, the milk was supplied *ad libitum;* as soon as the containers were emptied, these were refilled. During our preliminary trials, the experimental animals were given daily in addition to the milk, 10 gm. of a cooked cornstarch-agar-agar mixture, consisting of 15 per cent. cornstarch, 2 per cent. agar-agar, and 83 per cent. water. But since later work showed that defecation took place normally in the absence of this, it was discontinued.

RESULTS OF EXPERIMENTS

The growth curves of all animals fed milk boiled one minute and ten minutes, respectively, are surprisingly uniform (Charts 1 and 2). In no case, however, do these conform to the normal growth curves as given by Osborne and Mendel and McCollum and Davis. During the first six weeks of the diet, growth was apparently normal. From this time on, the weight curves show little or no gain. The curve of growth of those animals fed milk boiled forty-five minutes (Charts 2 and 3) show considerable variation; none of these, however, is in accord with the normal growth curve. This variation, we believe, is explained by the fact that during the early part of the investigation we had some difficulty in keeping the rats from killing one another. On several occasions, small portions of the dead animals were eaten. Those animals (Chart 5) fed milk heated during forty-five minutes at 114 C. grew for a short time at about the same rate as those animals given milk heated to the lower temperature. Nutritive disaster, however, was much more sudden. All animals fed this diet exclusively, died within eleven weeks of the beginning of the experiment, whereas

3. The process involved consisted in heating the milk to 83 C. by passing it over heated drums and then cooling it immediately.

the animals which received milk heated only to the boiling point lived many months. But what is even more significant than the slow growth, is the fact that we never had reproduction with any of our experimental animals fed boiled milk, although many were long past the period of sexual maturity, and in many cases, their weight was greater than our normal animals which were reproducing.

The value of raw milk as a food which meets all the nutritive requirements for growth and reproduction has been shown by various investigators. McCollum[4] fed a pig for a period of 395 days on raw cow's milk. It grew from a 23-pound animal to one weighing 406 pounds. During this time the sow gave birth to two dead and eight living young, each weighing from 2 to 3 pounds. The latter were suc-

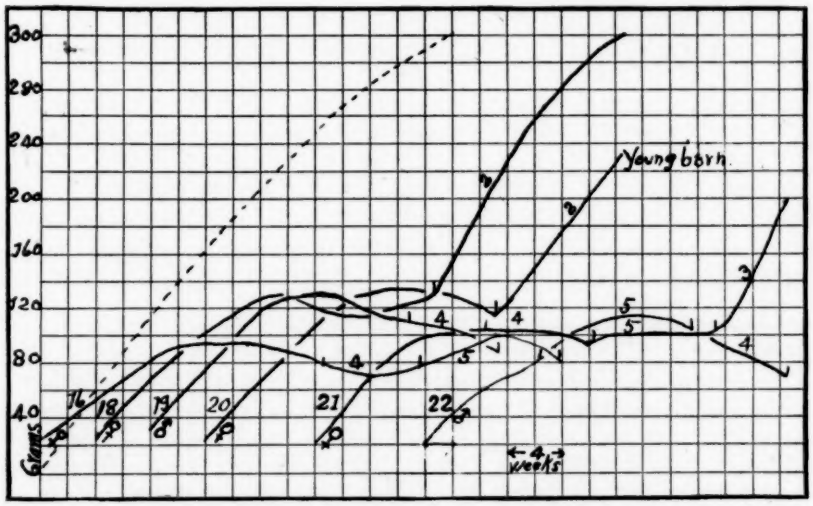

Chart 1.—Curves of growth of rats fed milk boiled one minute. Rats 18 and 20 (Period 2) show the influence of the addition of small amounts of egg to the diet. The addition of casein from boiled milk also caused growth to be resumed. (Rat 21, Period 3). The addition of neither 6.5 per cent. sucrose (Rats 16, 19, 21 and 22, Period 4), nor of dextrimaltose (Rats 16, 21 and 22, Period 5), caused an appreciable increase in weight. The curve of normal growth is represented by the broken line.

cessfully suckled. Osborne and Mendel[5] state that in their "numerous experiments milk has proved to be an adequate food both for growth and maintenance. Young rats fed solely on a milk food which we have been accustomed to use, not only have grown from infancy to full maturity, but have also given birth to litters of normal young. . . . One must conclude from these facts that the milk food con-

4. Henry: Feeds and Feeding, 1912, p. 98.
5. Osborne and Mendel: Jour. Biol. Chem., 1913, xv, 313.

tains all that is essential for both growth and maintenance." The milk food referred to consists of a mixture of milk powder, starch, and lard. We infer that in these experiments in which the authors state that milk has proved to be an adequate food, milk powder was used. Wheeler[6] reports normal growth over a period of sixty

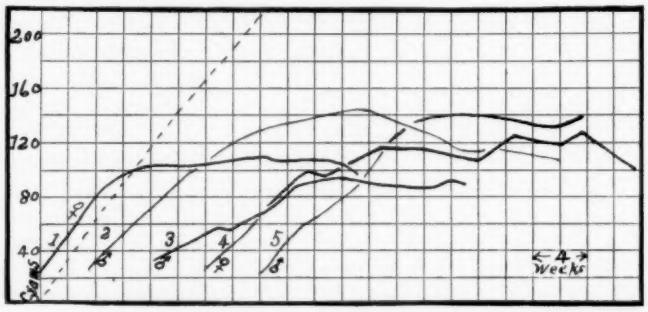

Chart 2.—Curves of growth of rats fed milk heated to 100 C. during ten minutes. The curve of normal growth is represented by the broken line.

days in mice fed raw cow's milk to which was added 6.5 per cent. sucrose. There are no records of reproduction with these mice, but we have no reason to doubt that, had the experiment continued longer, this would have taken place.

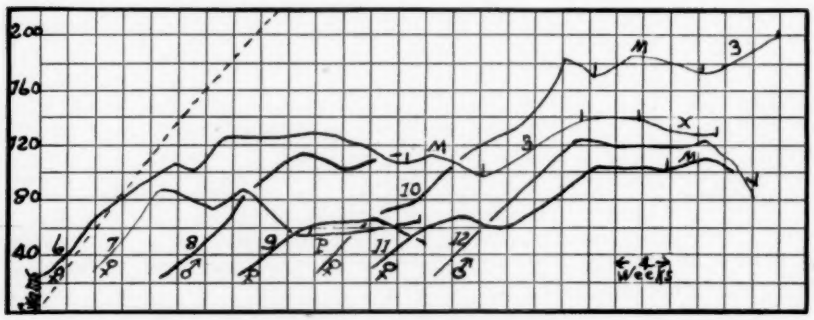

Chart 3.—Curves of growth of rats fed milk boiled forty-five minutes. The addition of casein from boiled milk caused growth to be resumed (Rats 6 and 10, Period 3). Pasteurized milk caused no improvement in Rat 7 (Period P). The addition of 6.5 per cent. lactose to the diet of boiled milk caused a slight increase in weight (Rats 8, 10 and 11, Period M), followed by a decline. The addition of meat extract to the boiled milk caused no gain in Rat 8, Period X). The curve of normal growth is represented by the broken line.

Up to the present we have been unsuccessful in our attempts to feed rats for any length of time on either raw or pasteurized cow's milk alone. Growth on raw milk took place much more slowly during

6. Wheeler, Ruth: Am. Jour. Dis. Child., 1915, ix, 300.

the early part of the growth period than with either boiled or pasteurized milk; in fact, we have been unable to keep rats alive on this diet. Three of a group of six on raw milk exclusively, died. Two others, apparently doomed, were given very small amounts of other food material—eggs, toast, fruit, etc.—in addition to the raw milk. Normal growth was at once resumed. Other rats fed raw milk to which was

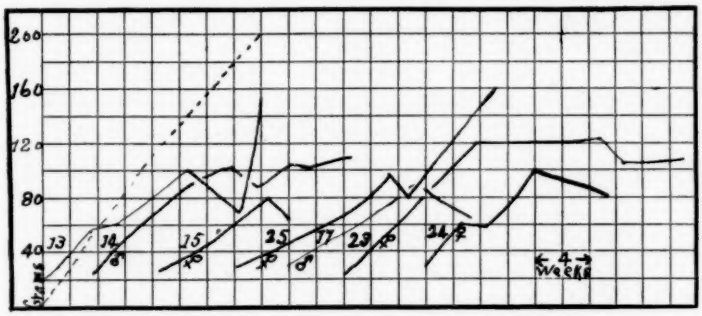

Chart 4.—Curves of growth of rats fed milk boiled forty-five minutes. The addition of well-washed egg yolk to the boiled milk diet caused growth to be resumed in Rats 13 and 25. The curve of normal growth is represented by the broken line.

added daily a small amount of beef extract (0.3 gm. per rat) grew at the normal rate (Chart 8, Rats 70, 72, 73, 74). Rat 71, the only female of the group, received raw milk for four weeks. During the third week there was no gain. Beef extract was then added to the diet; growth was at once resumed, and four weeks later this animal gave

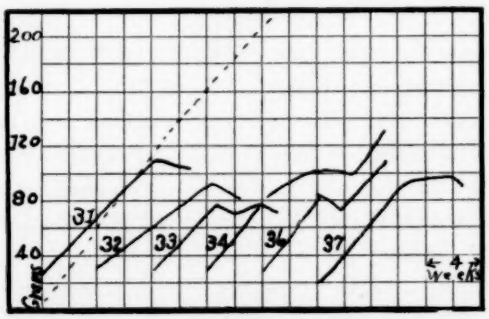

Chart 5.—Curves of growth of rats fed milk heated to 114 C. during forty-five minutes. The addition of egg yolk to the diet of Rat 36, and egg white to the diet of Rat 34, caused growth to be resumed. The curve of normal growth is represented by the broken line.

birth to two living young. These were successfully suckled. For three weeks following the weaning period two rats (Chart 7, Rats 64 and 65) were given raw milk plus small amounts of meat extract.

These were then transferred to the untreated raw milk diet and continued to grow at the normal rate for about four weeks. Following this, there was a decline in weight. Another raw milk animal (Chart 7, Rat 63) which was about to die, was given a mixed diet for three days and then returned to raw milk. Growth was at once resumed.

Those animals on pasteurized milk grew normally for about five weeks and then began to lose weight. Four died. Four others (Chart 6, Rats 42, 43, 44, 46) which were in the same moribund condition as those which died, were given small amounts of meat extract (0.3 gm. per rat) added to the pasteurized milk. Recovery followed and the animals continued to grow at the normal rate during the time of the investigation period.

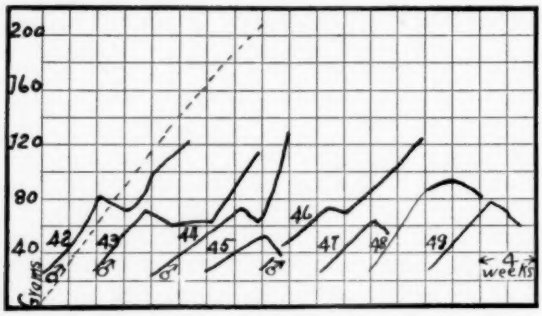

Chart 6.—Curves of growth of rats fed pasteurized milk. The addition of meat extract caused growth to be resumed. (Rats 42, 43, 44 and 46.) The curve of normal growth is represented by the broken line.

DISCUSSION OF RESULTS

We appreciate that criticism may be made to the effect that our animals were not kept under strictly aseptic conditions and that our failure to raise rats on either raw or pasteurized milk exclusively may be due to bacterial invasion. The results cited above, however, show that such cannot be the case, for all of our animals were kept under the same conditions. Apparently raw cow's milk is not well borne by young rats. By boiling, the milk has been made more digestible, but at the same time it has been chemically so changed as to render it an inadequate food. These results are comparable with those of other investigators who have shown that boiled milk of another species may be better borne than raw milk of another species. The milk powder used by Osborne and Mendel was apparently in such form as to be easily digested.

The part played by the beef extract in increasing the nutritive efficiency of raw and pasteurized milk is not clear. Obviously, the

increase in weight of our animals is much more than can be accounted for by the increase in the calorie value of the food ingested. Furthermore, the addition of the same amount of the extract to boiled milk caused no increase in weight during the brief experimental period—two weeks (Chart 3, Rat 8). It is well known that this material contains measurable amounts of amino-acids and inorganic salts, as well as very small quantities of soluble proteins, and the so-called extractives of muscle. But we can hardly believe that milk is deficient in those amino-acids essential for growth; nor can we think that the inorganic material is insufficient, since such noteworthy results[7] have been obtained in investigations in which the mineral content of the food has been similar to that of milk. It is probable that the explana-

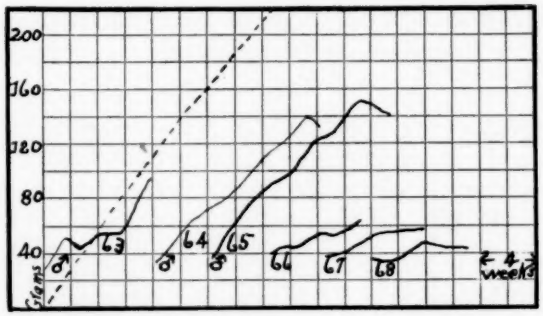

Chart 7.—Curves of growth of rats fed raw milk. Rats 64 and 65 received raw milk plus small amounts of beef extract during the first five weeks. From this time raw milk only was given. Rats 63 and 66 received a mixed diet for three days following a raw milk diet; the raw milk diet was then resumed.

tion lies in the well-known fact that the extractives of meat increase the digestive secretions, more particularly the gastric juice, and that both the raw and pasteurized milk have been made thereby more available. Experiments now in progress in this laboratory are aimed to determine this point. In the meantime, one is led to speculate as to what would be the effect of adding small amounts of meat extract to the diet of infants who are having difficulties in digesting raw cow's milk.

The failure of our rats to grow normally and reproduce when fed milk heated to a temperature of 100 C. or over, is undoubtedly due to the destruction, at least in part, of one or more of the essential constituents of milk. There is considerable evidence that high temperatures bring about definite chemical changes in the proteins of the milk.

7. McCollum and Davis: Jour. Biol. Chem., 1913, xv, 167.

Rettger[8] found that on heating milk above 85 C. a partial decomposition of milk protein occurs, resulting in the liberation of volatile sulphid. Earlier work by Schulz[9] showing that one of the sulphur cleavage products of albumin, namely, cystin, gave off only part of its sulphur by boiling with alkali, suggests that in the process of heating milk some of the cystin is destroyed. It is possible that the chief protein of milk is somewhat deficient in this essential amino-acid; when some of this is destroyed by heating, there is too little left to furnish the adequate amount for growth and reproduction. This theorem is further enhanced by the work of Osborne and Mendel.[10] These investigators have shown that rats can be maintained on a very much smaller amount of casein as the sole protein in an otherwise adequate diet if cystin is added. Our experience seems to bear this out. Two rats (Chart 1, Rats 19 and 20) which had ceased to grow on milk boiled one minute, were given daily in addition to the regular diet 13

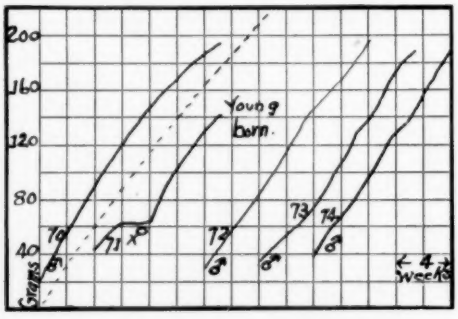

Chart 8.—Curves of growth of rats fed raw milk. Rat 71 received raw milk for four weeks following the weaning period; from this time a small amount of beef extract was added daily to the raw milk. Rats 70, 72 and 73 received raw milk and beef extract during the entire experimental period.

gm. of hard cooked egg. Within a very few days there was a marked improvement in appearance. Rapid growth then followed and the female, two months later, gave birth to a litter of eleven young. Hard cooked egg yolk, from which all soluble material had been removed by repeated washing, was as efficient as the whole egg in correcting the deficiency of heated milk (Chart 4, Rats 14 and 25). The addition of casein, precipitated from boiled milk and having a protein content equivalent to nearly twice that supplied by the egg, also caused growth to be resumed (Chart 3, Rats 6 and 10; Chart 1, Rat 21). Up to

8. Rettger: Am. Jour. Physiol., 1902, vi, 450.
9. Schulz: Ztschr. f. physiol. Chem., 1898, xxv, 16.
10. Osborne and Mendel: Jour. Biol. Chem., 1915, xx, 351.

the present time—eight weeks after the beginning of the casein diet—we have had no reproduction in these rats. It appears, therefore, that the protein of egg is more efficient as a corrective of the defects of heated milk than is an increased amount of casein. Nevertheless, we must not fail to appreciate that there may be other contributing factors, such as the inorganic materials, growth determinants, etc., present in the egg yolk or present in larger proportions than in the casein. The practice among some pediatrists of feeding babies with boiled or pasteurized milk mixtures having a higher protein content than is usual for raw milk feeding, is noteworthy in this connection. Also the practice of introducing egg yolk into the diet of infants fed on cooked cow's milk at an earlier age than those fed on mother's milk, is apparently justified.

The increase in weight in our animals to which small amounts of egg, in some cases, and casein in others, were added, might seem to be explained by the increase in the caloric value of the food ingested. Experiments aimed to determine this point were tried. To the diet of rats fed boiled milk was added 6.5 per cent. sucrose, 6.5 per cent. lactose, and 6.5 per cent. dextrimaltose, respectively. The very slight and not well sustained increase in some cases (Charts 1 and 3, Rats 16, 18, 8, 10 and 11) and the lack of increase in others (Charts 1 and 3, Rats 19, 21 and 22) show that this cannot be the explanation. Moreover, the fact that rats can grow normally and reproduce on raw milk to which small amounts of meat extract are added, indicates that the animals are able to ingest enough milk to fulfil physiologic requirements.

SUMMARY

Our results point to the conclusion that milk heated to the boiling temperature or thereabouts is an inadequate food. Rats fed on boiled milk grew to about half their normal size. Although we have been able to keep these experimental animals for many months on boiled milk, in no case have we got reproduction, nor have any of our animals reached the normal weight for adult rats.

Milk which is kept at the boiling temperature for forty-five minutes is no less efficient as a food than milk boiled for much shorter periods —ten minutes or one minute. The chemical changes which make heated milk an inadequate food are brought about at the boiling temperature or thereabounts. The value of pasteurized milk as a food, therefore, will depend on the temperature to which it is heated during the pasteurization process. Heating milk to a higher temperature than boiling (114 C.) makes it even less valuable as a food.

Although boiled cow's milk is an inadequate food for rats, it is apparently better borne than raw or pasteurized cow's milk, for we have been unable to raise young rats on either exclusively. However, rats fed both raw and pasteurized milk to which small amounts of meat extract were added grew at the normal rate. The explanation of this lies, possibly, in the fact that the meat extract caused an increase in the digestive secretions, thus making the milk more available.

The advantage of using raw milk for infant feeding is obvious. When babies are unable to digest raw cow's milk, however, or there is danger that the milk may be contaminated, we believe that the pediatrist is justified in using boiled milk. When this is given, the mixture should have a higher protein content than when raw milk is used.

CONGENITAL SYPHILIS, SIMULATING MONGOLISM, IN ONE OF TWINS *

FRANK VAN DER BOGERT M.D.
SCHENECTADY, N. Y.

Recently three children were presented at the Children's Dispensary of Schenectady. Two were, to all outward appearances, of the Mongolian type. The third, a twin of the younger, apparently perfectly normal.

The father and mother are seemingly healthy Italians, not of the lowest class. There had been no miscarriages, but four children in all, the fourth said to be well. A history of syphilis in the parents was not obtainable.

The mother's age at the time of birth of the older child, now 9 years, was 18. The second, now 8, was born when the mother was 20. The twins, 5 years old, one normal, the other diseased, were born when she was 22.

These ages of the mother at the time the several births occurred are mentioned because mongolism is likely to show itself in the offspring of women of advanced age, of women who have borne many children, or of young women in whom the reproductive functions have not been fully developed.

The mother was neither old nor was she worn out by numerous pregnancies when the twins were born, but the first child showing evidence of the mongol, was born when she was comparatively young.

The similarity in appearance of some cases of congenital syphilis to mongolism has been suggested, though not very generally realized.

Still[1] says that in his experience the two conditions most commonly confused in the diagnosis of the mongol have been cretinism and congenital syphilis, and calls attention to the existence of snuffles and the flattened bridge of the nose in both the congenital syphilitic and the mongolian idiot.

About a year ago the two diseased children were shown before a clinical meeting and all present admitted them to be typical mongols. A careful study and physical examination of the diseased twin, however, leads one to believe that he is not a typical mongol.

At first sight the face is characteristic but on analysis of the features the broad, flattened nasal bridge is all that is distinctive. The palpebral fissure is narrow, but there is slight if any slanting. The mouth is held slightly open, but the tongue does not protrude. The tongue shows no distinct enlargement of papillae, nor is it fissured. The head is not flattened anteroposteriorly and the circumference is practically normal. There is no blepharitis, no heavy or

* Submitted for publication Nov. 1, 1915.

1. Still: Common Disorders and Diseases of Childhood, London, 1910.

snorting respiration. The hands are not characteristic of the mongol. The child gives a history of irregular teething and there is a slight heart lesion, but these conditions are not peculiar to the type.

As to his mental condition, he is said to be brighter than his apparently normal twin brother.

Conclusive evidence of syphilis is found in dwarfed stature, a large liver palpable 3 inches below costal margin, a spleen extending nearly to the crest of the ilium below and nearly to the navel in front, and a positive Wassermann.

During the examination an interesting condition of the fingers was noted, the cuticle merging with the dorsal surface of the nails with no line of demarcation at the junction. This condition was not present on the toes.

Twins reported on by author, showing difference in development and mongolian features of smaller.

The blood showed, Oct. 4, 1915, reds, 2,680,000; whites, 10,200. I quote from the report on the smear which was made by Dr. W. B. Stone, pathologist of the Schenectady Laboratory Association:

"Not knowing the other features of the blood examination, I can only give the features of the stained smear. There is a very great variation in size of the various red corpuscles, and also a marked degree of poikilocytosis. There is a slight degree of polychromatophilia and I found one normoblast. The large cells are more numerous than the smaller ones. This is evidently a grave anemia and quite suggestive of the pernicious type, which is very rare in children; some do not admit its existence. Syphilis and rickets and other conditions, however, sometimes produce a blood picture similar to this."

The urine is negative as to albumin and sugar and contains no bile.

The mongolian effect is added to by a decided yellow tinge of the skin undoubtedly due to the anemia.

Most interesting is the fact that the twin brother, apparently well developed and many inches taller, gives a negative Wassermann.

Although no Wassermann has recently been made on the blood of the first child, who also shows the mongolian features, I understand that a positive reaction was obtained within the past twelve months.

This first child possibly conforms more nearly to the mongol type in that the head is somewhat flattened from behind forward and the circumference is possibly less than normal.

The nasal bridge is broad and the eyes slant slightly. The hands are stubby. She is 9 years old and has reached but the second grade in school, evidently of slow development mentally.

Her liver is markedly enlarged and the lower margin of her spleen disappears under the crest of the ilium.

The importance of syphilis as a direct causal factor in the production of mongolian idiocy has been suggested. There is, however, no evidence of more than an indirect relation, as suggested by Still,[1] through rendering the reproductive organs imperfect. Thomson[2] says there is no reason to think that congenital syphilis or alcohol has anything to do with the symptom.

The main interest in these cases lies in the following facts:

1. Syphilis has shown itself congenitally in one of twins and has left the other apparently uninfected.

2. They emphasize the likelihood of mistaking syphilis for mongolism.

The similarity of the symptoms of the two conditions has probably been responsible for the belief that syphilis may directly cause the defect.

The accompanying photograph shows well the difference in development of the twins and the mongoloid features of the smaller.

111 Union Street.

2. Thomson, John: Clinical Examination and Treatment of Sick Children, Edinburgh, 1908.

CLINICAL DEPARTMENT

TRAUMATIC RUPTURE OF THE LEFT KIDNEY*

CHARLES J. BLOOM, B.Sc., M.D.
AND
RUSSELL E. STONE, M.D., F.A.C.S.
NEW ORLEANS

INTRODUCTORY

The case we are to report is of interest both to the clinician and to the surgeon. Our main reasons for presenting same are twofold: first, on account of the rarity of these cases, and, second, because there were no objective manifestations of trauma.

Kuster, in 7,741 injuries at the clinics of Baser and Berlin, tabulates only 10 cases of injuries to the kidney, or a little more than 1:1,000. Of these 10 only one was similar to the case now to be presented. Of 2,610 autopsies under his supervision, there was only one of a penetrating nature. Israel reports only one operative case, notwithstanding his large experience in renal surgery.

REPORT OF CASE

Family History.—Irene C., aged 11 years, was the fifth child of six living children. Her father and mother give a negative history in every detail, and her family history with reference to tuberculosis, malignancy and insanity was negative.

Previous History.—Born at 9 months, normal delivery. Breast fed entirely for one year, and with soft food until she had reached the age of 32 months. From that time on she had received full diet. Prior to her present illness she had never needed the attention of a physician.

Present Illness.—In the forenoon, Aug. 5, 1915, while the patient was standing on the edge of a wagon, with one foot balanced on a swinging gate, her little brother pulled the gate in the opposite direction, causing her to fall. In falling it is evident that she traumatized the middle and left lower quadrants of her body. Following this, she fell from the wagon to the ground, a distance of about 3½ feet. She was unconscious for a few minutes, and after regaining her senses, complained of a "pain in her stomach" and about fifteen minutes later vomited. At 8 p. m., on the same date, she voided "a black urine," and at 9 p. m. had about 1 degree elevation of temperature. During the night she voided three times, the urine becoming clearer as time progressed. The following morning, Aug. 6, 1915, she had "frequent desire to urinate," however, unaccompanied by pain. She complained of a "drawing down pain" radiating from the region of the stomach to the vicinity of the kidney. She was admitted to Hotel Dieu at 9:15 p. m., August 6, her father having brought her there from Kenner, La.

* Submitted for publication October, 1915.

Physical Examination.—Well nourished, and fairly well developed. A careful inspection of the abdomen made by Dr. Stone and myself revealed some degree of tympanites, and a slight sensitiveness to touch. Other than her temperature being 102, pulse 136, respiration 34, there were no external manifestations of traumatism.

Laboratory Reports.—Total white count, 13,500; 77 neutrophils, and 33 small mononuclears. August 7 the urine had a specific gravity of 1.024, was acid in reaction and contained no albumin or sugar. A few hyaline casts were present, also a few red blood pus and epithelial cells, and cylindroids. August 10 the urine report was: Specific gravity 1.010, acid reaction, no albumin, or sugar; many red blood cells, and few pus cells; no casts or crystalline deposits.

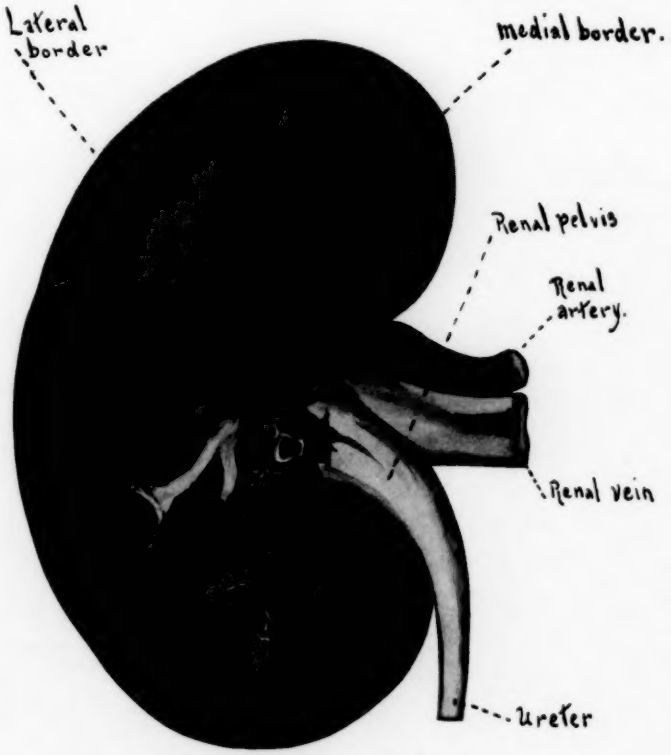

Fig. 1.—Drawing of ruptured kidney.

She was kept under observation twenty-four hours, but with an increased temperature, a weakened pulse, a certain amount of shock, a leukocytosis, with an increased amount of tympanites, and abdominal sensitiveness, a diagnosis of rupture of the left kidney was made, and we came to the conclusion that surgical interference was necessary.

Operation.—The operation was done under ether anesthesia, administered by Dr. Caine. The incision was made completely from the twelfth rib to the crest of the ilium. A large hematoma, firmly organized, was found, and this was removed with some trouble. On examination of the kidney we found two separate lacerations: one at the lower pole, the other about 3 inches above. The capsule was completely torn away, and in shreds; hence it was quite

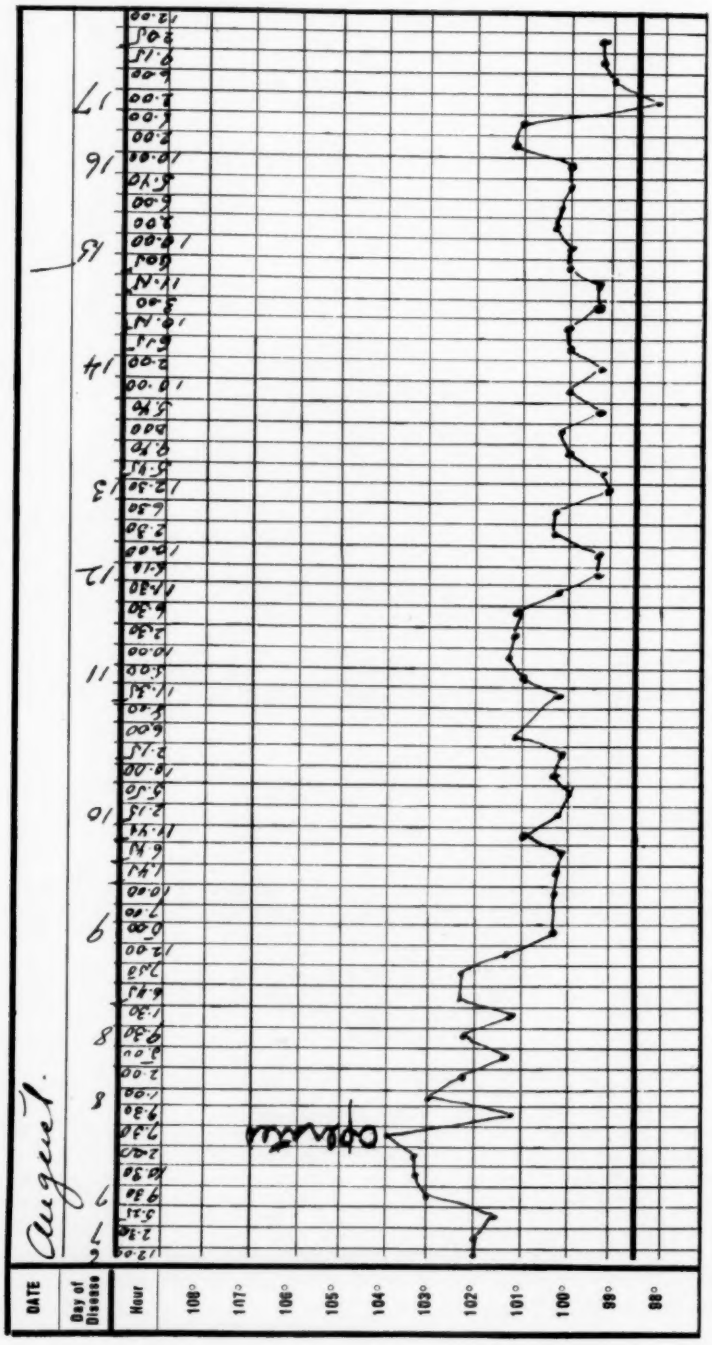

Fig. 2.—Chart showing temperature curve of authors' patient.

impossible to suture the kidney. The field was irrigated with a saline solution, and a large cigarette drain introduced and the wound closed. The operation consumed thirty minutes, and as the pulse was 188 at the beginning of the operation, and 200 at the end, it was necessary to infuse the patient with 600 c.c. saline solution. The patient reacted nicely and improved daily until her discharge from the hospital on the ninth day. Drainage was removed on the fifth day, and urine from the wound discontinued on the seventh day.

Considering traumatic injuries of the kidney, the symptoms present in the majority of cases are, first, pronounced shock; second, pain in the lumbar region, particularly in the costovertebral angle, often radiating along the ureter to the region of the bladder, and hematuria of varying degree. In this case, although there was an external hemorrhage, the tumor mass which is sometimes seen, was absent. According to Tuffier, the injury in this case was one of the third degree: one in which the capsule was ruptured; in which there was an extra renal hemorrhage, with two deep, multiple, stellate fissures of the kidney substance, most pronounced below the hilum.

PROGRESS IN PEDIATRICS

RECENT ADVANCES IN ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF CHILDHOOD*

JAMES B. HOLMES, M.D.
BALTIMORE

N. Pende[1] has described what he believes to be a new endocrinal gland. The structure has been found by him in puppies and in infants under 1 year of age. It occurs in the form of fifteen to twenty solid "epithelial islets," scattered around the parathyroids, thyroid and upper pole of the thymus, occasionally, also, at the lower pole, and more especially in the connective tissue of the superior outlet of the thorax.

These structures were found in making serial sections of the neck organs from the tongue downward. The author thinks it is not improbable that the glands have also a wider distribution.

In newlyborn infants the largest masses may be seen, at times, as grayish red points that through their richness in vascular capillaries stand out against the suprathymic or periparathyroid connective tissue.

The conformation of the islets is said to be microscopically quite characteristic. They consist of a mass of closely packed cells pierced by a rich capillary plexus, and almost always lacking any firm connective tissue stroma.

The masses have no capsule but are separated from the adjacent structures by loose connective tissue in such manner that the individual groups of cells appear, microscopically, as true, sharply defined, islands.

The individual cells are large, having two or three times the circumference of the parathyroid cells in the same individual. They are described as having the appearance of epithelial cells, being round or polygonal in form, with very definite margins to the protoplasm, and having a very large, centrally placed, round epithelioid nucleus, with a delicate nuclear membrane, a scanty chromatin network and several nucleoli. In many cells the nucleus is smaller, homogeneous, and

* Submitted for publication Nov. 7, 1915.

1. Pende, N.: Ueber eine neue Druse mit innerer Sekretion (Glandula insularis cervicalis), Arch. f. mikroskop. Anat., 1914, lxxxvi, No. 1, p. 193; also Riforma med., 1913, No. 22.

deeply-staining. The cytoplasm consists of numerous small granules so thickly placed that the protoplasm often appears to be stained homogeneously.

In a small number of cells there are seen scattered, larger, drop-like granules which stain well with eosin and other acid stains, but poorly with basic stains. In many cells the protoplasm has a vacuolated appearance. Such cells are met infrequently in the newly born, but their number increases rapidly with increasing age, and especially, says the author, under pathologic conditions. By the end of the first year there is visible a more or less large mass of vacuoles in practically all the cells. These vacuolated cells show then a small pyknotic, accentrically-placed nucleus of variable size. The after fate of these cells, and the evolution of the islands generally, has not yet been studied; further investigation is in progress.

By applying Ciaccio's method of staining for lipoids, Pende has found that most of the granules are lipoidal in nature. As vacuolization proceeds, true fat globules appear in the place of these lipoid granules with increasing frequency. No pigment granules or other metaplastic structures such as glycogen granules are seen. The chromaffin reaction is negative.

No glandular lumina, cysts, follicles, or enclosed colloidal spaces are present. For this reason Pende thinks that the bodies are not remains of the so-called *post-branchial bodies* on the one hand, nor rudimentary portions of the adjacent glands of epithelial origin, the thyroid, parathyroid and thymus, on the other. The structure of the islands is quite different from that of the last mentioned glands.

The author's statement that these new glands of internal secretion remind one in detail of the appearance of the suprarenal glands, is noteworthy. There are many points about the above description of the new gland that may be applied to the appearance of embryonic fat, and masses of this, it will be recalled, are often met about the poles of the kidneys in the newly born, and in their resemblance to the suprarenal glands, have not infrequently caused confusion.

Prof. Pende is First Assistant in the Institute of Medical Pathology at Palermo. The result of his further studies, which are now in progress, will be awaited with much interest. Excellent plates accompany the present report. A brief, earlier report was made in the *Riforma medica,* 1913, No. 22.

During the past year two studies have been made bearing on the nutrition of infants. Benestad[2] has subjected the problem of initial loss of weight in the newly born to further analysis. Carlson and his

2. Benestad, G.: Wo liegt die Ursache zur physiologischen Gewichtsabnahme neugeborener Kinder? Jahrb. f. Kinderh., 1914, lxxx, No. 1, p. 21.

collaborators have utilized the reappearance of gastric contraction-waves in the infant to determine the proper interval of feeding.

The initial loss of weight in the newly born has long been known. Scientific attention was directed to it about a century ago by Chaussier, and the fact now finds appropriate statement in all textbooks of pediatrics. The loss begins promptly after separation of the child from the mother and continues until, on the average, one fifteenth to one seventeenth of the original body weight is lost. The recovery from the loss begins usually about the third or fourth day after birth. During the next week the infant recovers its original weight, i. e., by the end of the tenth day.

This phenomenon is not peculiar to the human species. It occurs in some other animals, e. g., guinea-pigs (Edlefsen). It does not occur, or is a very infrequent phenomenon in dogs, cats and rabbits (Kehrer).

As shown by L. Faye, in 1874, the loss consists largely in water, by means of the insensible perspiration, the respiratory loss, the very considerable water content of the meconium, and the scanty urine.

During the first two or three days Nature does little to supply this loss. The child receives only a small amount of colostrum (100 c.c.) to oppose a relatively large loss of fluid.

Some years ago it was reported that this initial loss could be prevented by supplying the child with food during the interval elapsing before the maternal supply appeared, and recently Bailey and Murlin[3] have recommended feeding newly born infants, in addition to the breast secretion, a formula of about the same composition as colostrum.

If this initial loss of weight is a normal and inevitable phenomenon it must be accepted as such. Clearly the meconium is an accumulation formed in the intestines during the course of development. It may be regarded as waste material, and no more a true part of the newly born infant than the vernix caseosa. If so, the average weight of this substance might properly be deducted from the average birth weight—about 200 gm.—which, together with the urine voided, would be about one-half the total loss. The older texts taught that the colostrum was laxative in its action on the infant and was Nature's provision for freeing the organism of the meconium. It is not inconceivable that some other part of the initial loss of water may represent a necessary riddance. If the initial loss is necessary or inevitable the pediatrist must be tolerant of it and he may solace himself with the thought that the true loss of weight is not really so great as it seems.

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3. Bailey and Murlin: Proc. Soc. Exper. Biol. and Med., 1914, xi, 109.

If, however, the phenomena of the early days of lactation, the production of colostrum and the delayed appearance of milk constitute another imperfect adaptation on the part of Nature, then clearly the attending pediatrist may hope to render the adaptation more perfect. He may supplement the existing provision for supplying fluid to replace that which is being lost. He may feed the child in the interval that elapses before the natural supply of food becomes available.

Benestad has reviewed these points. He finds that the extent of the loss of weight depends, (1) on the degree of development of the infant, (2) on the actual weight at birth, and (3) on the milk supply of the mother. Another factor that is less frequently operative seems to be great loss of blood in the mother (presumably through subsequently diminished milk flow). The severity of the birth process does not in itself appear to be a factor.

The studies of numerous workers (Winkel, Gregor, etc.) have shown that premature infants lose proportionately more weight than full-term infants. This is true even when the latter are small infants at birth (3,000 gm.). The percentage of the birth weight lost decreases with the maturity of the infant. This, the author thinks, is due to the greater deficiency of the digestive apparatus in the mature child.

Newer studies have shown that the more important enzymes are present in the digestive tract of viable premature infants. Formerly it was believed that many enzymes were not present until some weeks after birth. Langstein and Soldin have found erepsin as early as the thirtieth week. The demonstration of the mere presence of these enzymes does not prove, however, that they are present in quantities sufficient for the digestion of the volume of food received by a young infant from its mother.

The failure of all efforts to prevent the initial loss of weight, says Benestad, or even appreciably to diminish it, by supplying newly-born infants with milk from wetnurses, whose children are but a few days older than the patient, seems to indicate a functional inability to utilize the milk during the first days of life, even in a mature infant. Forcing food at this time may even delay the normal recovery of the birth weight (Altherr).

An initial loss of weight is not present, or is very transitory, in most mammals that have been studied. The period of infancy also is shorter in all other animals than the human species. It would be but in accord with this if it were found that the digestive functions were more complete at birth in young animals than they are in the human young. Bahrdt and Langstein's studies show that the calf possesses the power to reduce albumin to amino-acids, even in the first days of

life. Simon's studies led him to the conclusion that in the human infant the breaking down of the albumin molecules stopped at the polypeptid stage, instead of proceeding to the amino-acids and ammonia. These polypeptids formed 10 per cent. of the total nitrogen output in the urine of the first few days, or double the percentage found in the adult. The percentage gradually diminishes and reaches normal by the end of the first week, the proportion of amino-acids and ammonia rising. It would seem that the human infant in contrast with the young of other mammals (for example the calf) is unprepared during the first days of life completely to digest albumin. Similar comparative studies have not been carried out on premature infants. They are, presumably, still less prepared to digest albumin. During intra-uterine life the organism is supplied by the products of maternal digestion—serumalbumin, sugar, and human fat. A shorter or longer period is required for adjustment to the conditions of extra-uterine life in which the organism must itself break down the higher compounds and elaborate them anew. Some days are, as a rule, necessary; the period is longer, or the process less rapid, in the case of premature infants. This period of defective digestion may be accompanied by a period of defective assimilation; the two can scarcely be separated.

Where infants are of the same degree of maturity the average initial loss varies with the birth weight. Infants weighing 3,000 gm. lose, on the average, 175 ounces (5.36 per cent.) during the first three days, while those weighing 4,000 gm. lose, on the average, 252 gm. (5.91 per cent.). As is seen, the difference in percentage loss is not great. It has not been shown on what this small difference depends.

Finally, the initial loss of weight depends on the milk supply of the mother. The most suitable food for the young infant is colostrum. Its fat and its serumalbumin are closely related to those to which the infant has been accustomed in its intra-uterine life, and if not fully broken down in the immature digestive processes are perhaps less liable to prove toxic. No other food can wholly replace it. With improvement in the digestive processes an increasing supply of mother's milk becomes necessary. In the meantime, says the author, artificial feeding increases and prolongs the initial loss of weight.

Williamson[4] has recently repeated and extended the early work of Leichtenstern (1878) on the hemoglobin content of the blood of the newly born. He examined over 900 patients ranging in age from 1 day to 76 years, and over. He employed the spectrophotometric method and the principle of extinction coefficient as developed by

4. Williamson, C. S.: Influence of Age and Sex on Hemoglobin. A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases (Preliminary Report), Jour. Am. Med. Assn., 1915, lxv, 302.

Vierordt and Hüfner. Details regarding the method and the author's application of it may be found in the original publication. Only that part of the work that relates to infants and young children will be discussed here.

The infants and children examined were as follows:

TABLE SHOWING NUMBER OF CHILDREN EXAMINED AND THEIR AGES

Age	Number of Cases		
	Male	Female	Total
1 day	16	15	31
2- 3 days	15	16	31
4- 8 days	15	18	33
9-13 days	15	15	30
2 weeks-2 months	15	15	30
3- 5 months	16	16	32
6-11 months	18	15	33
1 year	18	16	34
2 years	16	17	33
3 years	15	16	31
4 years	16	15	31
5 years	17	18	35
6-10 years	18	15	33
11-15 years	17	20	37

The material for the study was selected with care, effort being made to include only strictly normal, healthy individuals. The great majority of the babies were breast fed and all were thriving and gaining weight in a normal manner. A considerable proportion of the older children were school children and were studied early in the fall just after the closing of the summer vacation, and when their physical condition was presumably at its best.

The course of the hemoglobin percentage may be seen in the accompanying Chart 1.

After birth the percentage of hemoglobin begins to diminish at once, and after two weeks the decline is very rapid. By the fifth month the average value is very nearly down to the minimum (about 10/17 the value at birth) and far below the average value at 16 to 20 years (adult value). There is seen a very slight further decline at about 1 year, and thereafter a steady increase until the normal value is reached at 15 to 16 years. Thereafter there are but slight variations, with, toward old age, a slow decline.

The rapid decline in the amount of hemoglobin during the first five months is a highly characteristic feature of the age curve, says the author.

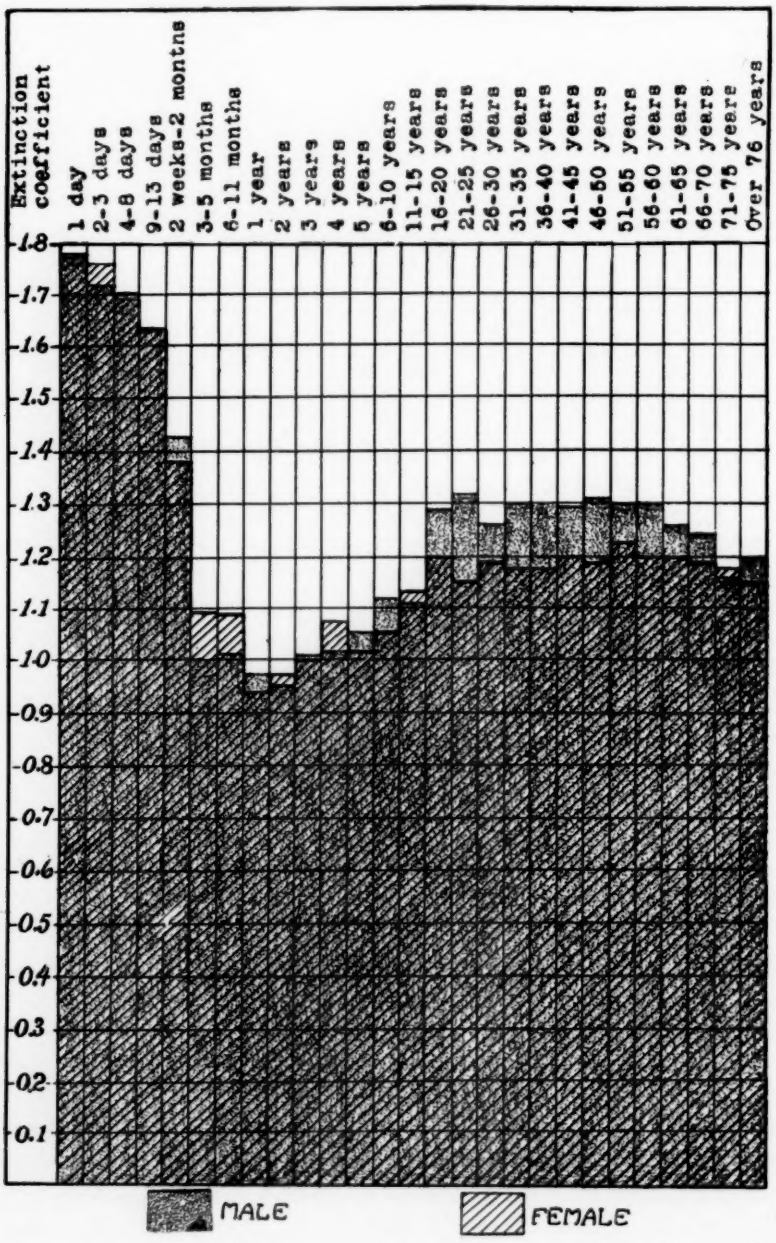

Chart 1.—Curve showing influence of age and sex on hemoglobin percentage. Shaded areas indicate males; diagonal lines, females.

In selecting the material an effort was made to have the two sexes equally represented in each age period. A comparison of the hemoglobin values obtained shows that up to the fifteenth year the hemoglobin content of the blood is almost precisely the same for the two sexes. After the fifteenth year sex differences make themselves plainly evident; the values for the women are, in every instance, considerably lower than those for the men; with age the difference grows less.

The practical conclusions that may be drawn from Williamson's work are:

1. Instruments which are graduated in percentages of a supposed average normal individual can not be utilized for making determinations in children of different ages without correction.

2. During the first two weeks the normal hemoglobin content of the infant is about 36 per cent. greater than that of the normal adult. Between the second and third months it just equals that of the normal adult and from the fourth month to the fourth year it is normally only about 80 per cent. of that of the adult (slightly less during the second and the third year.) The percentage rises gradually thereafter. No correction for sex is necessary.

3. Pediatrists should accustom themselves to allowing for the natural variations in hemoglobin at different ages.

The author gives the following example to illustrate the errors that may arise from disregarding these facts:

> Let us say that a mother who is 22 and a father who is 24, and two children, a boy of 1 year and a girl of 2 years, respectively, all being averaged as normal individuals, have their blood examined with any of the instruments which are graduated on the basis of an average normal adult. An inspection of the table with reduction to percentages, will make it evident that the values will be, father 100 per cent., mother 87 per cent., boy 1 year, 74 per cent., girl 2 years, 74 per cent. It thus appears that the mother is anemic to the extent of 13 per cent., and that both children are markedly anemic, to the extent of 26 per cent. The fact is that the mother and both children have the amounts of hemoglobin which they should have for the respective ages and sex. The anemia is merely apparent, and due to the fact that the hemoglobinometer was not calibrated to read in absolute terms, and that the physician did not take the age and sex variations into consideration.

Several papers upon congenital icterus have appeared during the current year. The most extensive and significant paper upon the subject is that from Arvo Ylppö[5] of Langstein's clinic. Ylppö reviewed the various theories of congenital icterus and our knowledge of the occurrence of biliary pigments in the blood, stools and urine, and restated certain methods that have been employed in the past in

5. Ylppö, A.: Icterus neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeboren, Ztschr. f. Kinderh., Orig., 1913, xi.

attempts to determine their presence quantitatively. He introduced the spectrophotometric method of determining the presence of biliary pigments quantitatively, and described the technic that he found applicable in the case of blood, urine and stools. He pointed out certain limitations of the method, but retained it as the most accurate method yet found. With it he investigated the secretion of biliary pigments in the fetus and the newlyborn, and the relation of the secretion to icterus neonatorum and icterus neonatorum gravis. He first took up the excretion of biliary pigments in the stools and urine.

His material consisted of 6 full-term infants that showed various degrees of icterus, 2 full-term infants that were not icteric, and 2 premature infants. All were examined throughout the first thirteen days of life and two full-term infants were examined between the eighth and twelfth week. One of the premature infants was reexamined in the sixth week.

The infants were placed in metabolism beds directly after delayed tying of the cord, and were kept there for thirteen days, being removed only for nursing. The meconium, the stools and the urine were collected separately and examined. A distinction between meconium and breast stool was made with the eye, or where this proved difficult, was established by the presence or absence, microscopically, of lanugo hairs. The infants were rated in four grades according to the amount of icterus present.

It was found that the weight of the meconium (dried, and in some instances freed from fat) obtained, varied from 0 to 23.23 gm., depending on the amount lost at birth, and that the biliary pigment contained in it averaged 22.5 mg. (0 to 63.43 mg.). The amount of biliary pigment obtained did not vary closely with the amount of meconium recovered.

In a later portion of his report the author established to his satisfaction that the placenta is an effective barrier against the passage of biliary pigments from the blood of the fetus to that of the mother. The amount of biliary pigments excreted during intra-uterine life may thus be estimated from the amount found in the meconium. This total Ylppö placed at about 33 mg.

He drew the following conclusion from his study of the excretion of bile pigments, stools and urine:

Up to the last month of intra-uterine life the formation of bile pigments is minimum. During the last month a striking increase may be demonstrated. During the whole fetal period there is in any case only about 33 mg. of biliary pigment excreted.

The increase in the formation of bile pigment which is recognizable in the last month of fetal life is definitely accelerated with the begin-

ning of extra-uterine life. From about the sixth day of life on, an especially rapid increase in the formation of bile pigment can be seen.

In the first thirteen days a total of about 140 mg. of bile pigment is excreted; of this, 0.5 to 1.6 per cent. (according to the intensity of the icterus) is excreted in the urine of icteric infants, and only minimal amounts, at most 0.1 per cent., is excreted in the urine of nonicteric infants. The total amount excreted shows no noteworthy difference between the icteric and the nonicteric children, and there is not a larger amount excreted in corresponding intervals in icteric infants.

There is no correspondence between the intensity of the icterus and the total amount of bile pigment that is excreted.

With these findings, the foundation, he says, falls from under all those haenatohepatogenous theories which refer icterus neonatorum to an absolutely large destruction of red blood cells in the icteric infant.

Ylppö then turned to the examination of the biliary pigment content of the blood. The circulating blood of normal adults contains a minute amount of bilirubin as Gilbert and Heracher have shown. Hammersten had shown that this is true also for the horse. Gilbert, Lereboullet and Stevens found that the amount is increased in the blood from the umbilical cord and from newly-born infants, as did Biffi and Galli.

Ylppö examined sixty-one children in this regard, including eighteen premature infants and two fetuses. The blood of some of these was examined from five to eight times, just after tying the umbilical cord and then at intervals during the course of the next few weeks. In some instances that of the mother was examined before, during and after childbirth. The findings are summarized thus:

The content of the fetal blood in biliary pigment is increased in comparison with that of healthy adults.

At the time of birth there is found a still more marked increase, which cannot be brought into relation with the conditions of birth (length, severity, etc.).

Those infants which have an especially high content of biliary pigments in the blood of the umbilical cord all become jaundiced, while those which have a strikingly small amount of pigment in the blood do not, as a rule, have jaundice.

After birth the content of biliary pigment in the blood rises in each child. This increase lasts three or ten days and varies in the rapidity with which it increases.

Children in whom the biliary pigment content of the blood exceeds a certain definite (but not sharply defined) *level for cutaneous jaundice,* become jaundiced.

The intensity of the cutaneous icterus shows a correspondence with the content of the blood in biliary pigment.

Infants in whom the amount of bile pigment in the blood ceases to increase by about the third day, and in whom the total content remains under the level for cutaneous icterus, do not become jaundiced.

Premature infants generally show the very high content of biliary pigment in their blood. This continues to increase ordinarily for six to ten days in them, and the amount of pigment in the blood remains above the level for cutaneous icterus for a week or more.

The result of Ylppö's clinical studies are summarized in the following sentences:

All viable premature infants (under 2,500 gm.) show icterus neonatorum: A great majority of them show a very intense icterus that lasts several weeks (forty-two of them were studied).

Eighty-two per cent. of the 355 full-term infants examined showed jaundice. They differed clinically from infants that did not show jaundice, only in so far as those in whom the jaundice was very outspoken, showed secondary symptoms, characteristic of cholemia (drowsiness, itching, etc.).

Three distinct forms of icterus neonatorum were distinguished: Icterus neonatorum simplex; icterus neonatorum prolongatus (duration over two weeks); icterus neonatorum gravis. Their unity was shown through the presence of all possible transitional forms and they are therefore to be looked on as being only various types of a single disease, icterus neonatorum.

This disease, icterus neonatorum, shows great independence in its course and is not influenced by secondary infections or trauma.

Data is then given to support the theory that there is in puppies an increase in the amount of circulating biliary pigments similar to that which appears in the human infant, but that it takes place in utero, and has almost or quite passed away at the time of birth. In the puppy the excess of pigment is laid down in granules in the placenta. In the human infant the phenomenon appears nearer the time of birth. A few granules of pigment may be deposited in the placenta (never any appreciable amount); the bulk of the pigment circulates in the blood until it is withdrawn by the liver or passes out in the urine (a small portion at most), and if present in more than a certain fixed percentage causes cutaneous icterus.

Only the horse and man show bilirubin in the blood normally, and only the young of these two mammals show icterus neonatorum.

The injection of bile pigment into the blood-stream of animals shows that in newly-born puppies and in adult dogs the liver quickly

removes the circulating pigment and passes it out as bile, minimum amounts only (much larger in the newly born) passing off in the urine. Administration of bile pigments by mouth yields no evidence, we are told, of the absorption of unreduced bile pigment from the intestine. Only man and the horse, says Ylppö, show bilirubin in their blood under normal conditions, and in these two animals only can it accumulate in the blood in the absence of injury to the functions of the liver.

As has been seen, Ylppö does not believe that infection plays any important rôle in the etiology of congenital icterus. When he began his work he thought infection played an important part. For this reason, he was especially watchful for any evidence pointing to a relation between infection and icterus in the cases studied by him. He found, on the contrary, that icterus neonatorum ran its course quite independently of infections, whether enteral or parenteral. (The infections whose influence was observed by him were aspiration pneumonia, tetanus neonatorum, umbilical sepsis, intestinal infection, and syphilis.) The fact that icterus neonatorum begins while the child is yet in utero would in itself weaken any theory of an infectious origin for it.

The fact that the percentage of circulating biliary pigment has already begun to increase before the time of birth, shows that the change is not dependent alone on postnatal circulatory changes, if it is dependent on them at all.

In the fact that the incompletely broken down albumin radicals are allowed to pass from the portal system of the newly born, through the liver, into the general circulation whence they are excreted in the urine, Ylppö sees further proof of functional immaturity of the liver in the human fetus at birth. As regards the maturity of their livers, the human young, he says, like the young of the horse, are born prematurely. And premature infants are, as regards the liver, doubly immature.

The mature liver when normally functioning secretes the bile into the bile capillaries. The fetal liver secretes its bile into the blood stream where it enters a closed circuit, very little of it being excreted in the urine in utero and little (in man) being laid down in the placenta. The excess is laid down in the liver itself. There is little excess, for little is produced.

Near the time of birth the liver normally begins to excrete bile into the bile capillaries. The more mature the liver is at the time of the birth of the infant, the more completely will it do this and the more perfectly will it keep the content of the blood in biliary pigments below the level at which icterus is produced. The less mature it is the less effectively will it do this and icterus neonatorum will appear in pro-

gressively severer grades. In the premature infant the liver is so immature that jaundice always results. In any case the depth of the jaundice (i. e., the content of the blood in biliary pigments) and the persistence of the jaundice are indicative of the length of time that passes after birth before the liver comes to the normal or necessary degree of functional maturity.

Such is Ylppö's theory of the etiology of congenital icterus. He portrays it schematically in the accompanying diagram (Fig. 2).

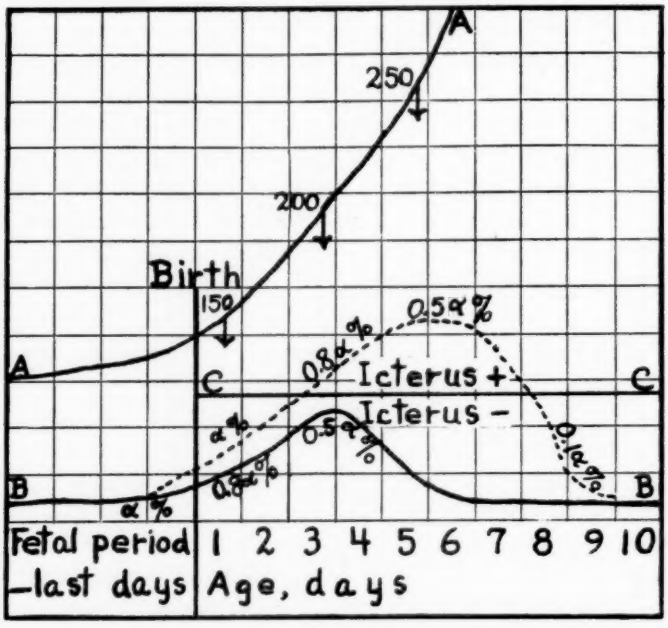

Chart 2.—Diagram of secretion of biliary pigment in icteric and nonicteric infants. Line A-A, pigment formed = 100 per unit of time; line B-B, percentage in nonicteric infant; C-C, level for icterus of the skin; dash line, percentage of pigment passing into the blood in icteric infant; solid line percentage in nonicteric infant.

In this diagram it is shown that there is a slow increase in the production of bile pigments per unit of time during the last days of intra-uterine life, and that this rate increases rapidly and continuously after birth. The older the child is, the more bile does the liver secrete, as is shown by the author's analyses. There is no rapid production of biliary pigment at or shortly after birth followed by a subsequent decline in production, as has often been assumed. It is inferred that any change noted in the count of the red cells of the blood or in the hemoglobin content of the blood at or near the time of birth is merely a concomitant phenomenon.

A. Hirsch,[6] of von Pirquet's clinic, reported a less extensive study of icterus neonatorum. She employed less accurate methods than Ylppö, but reached similar conclusions.

A more recent publication is that by Fridtzof Bang[7] of Copenhagen. Bang used the Gmelin-Gilbert-Sunde method of estimating bile pigments in the blood and reached results that are substantially in accord with those of Ylppö. His publication is chiefly of interest in its criticism of Ylppö's deductions.

Bang holds that Ylppö has not demonstrated in a conclusive manner that bile pigment discharged into the intestine may not be reabsorbed in part, and, passing around the liver through the *ductus venosus Arantii,* get into the general circulation.

Ylppö denied that there is any ***sudden*** increase in the percentage of bile pigment in the blood at or immediately after birth. Bang believes that there is such, and offers diagrams to prove it. He finds in this phenomenon proof that some new factor enters into the production of bile pigment at the time of birth. He theorizes as to what it may be.

Ylppö had attributed the accumulation of bile pigment in the blood of the newly born to a defective functioning of the immature liver parenchyma and held this was more marked in premature infants. Bang assumes that the fetal heart and the circulatory mechanism are at fault, and sees the cause of the abnormal biliary secretion in venous stasis.

At birth the pulmonary circulation is suddenly augmented, the placental circulation is interrupted. The heart of the newly-born infant is unable to adapt itself at once to the changed conditions. It needs time to make the adjustment. The regulating mechanism, cutaneous and other, is still imperfect, and stasis results in the liver and elsewhere.

As a result of stasis in the cutaneous capillaries, serum escapes into the tissues and the blood becomes concentrated, the hemoglobin index rises and also the count of red cells. As a result of stasis in the liver, the concentration of bile-pigment in the blood rises. It does this to a slight degree during stasis in adults (figures are given) and in infants the phenomenon should be more marked because the weight of the liver is relatively much greater with respect to the blood volume—56 to 77 instead of 28 to 77. As the heart gradually adapts itself to the changed conditions of circulation, the stasis passes away, and with it

6. Hirsch, A.: Die physiologische Icterusbereitschaft der Neugeborenen, Ztschr. f. Kinderh., Orig., 1913, xv.

7. Bang, F.: Recherches sur l'origine de l'ictère des nouveau-nés, Arch. mens. d'Obst. et de Gynéc., 1915, viii, 296.

the jaundice. The weaker heart of the premature infant requires longer to adapt itself, hence the jaundice persists longer.

The whole discussion is highly theoretical.

How often the healthy baby shall be fed and how much shall be given him at a feeding, are fundamental questions in pediatrics, yet there is no unanimity regarding this. Examination of recent textbooks and pediatric writings makes this clear. Great variety of opinion is expressed by leading teachers. The intervals advocated range from two hours for the first month to three, three and a half, and even four hours. Taken as a whole, American writers seem to prefer short intervals, while continental writers incline toward longer intervals. Some advocate shorter intervals in breast feeding, and longer ones in artificial feeding.

The normal healthy human infant, as the young of all animals, nurses when the sensation of hunger becomes strong enough to be uncomfortable, provided food is at hand at the time.[8] When careful records of nursing babies have been kept, it has been found that not only do the intervals between apparent inclinations to nurse vary greatly, but also the amount of food taken at a nursing varies. In the same child the length of the intervals may vary from 1 hour to 6 hours; the amount of milk taken at a nursing from 1 to 3 ounces, or more widely. Even when the child is placed at the breast at regular intervals he may yet vary the amount of milk taken at each nursing. These variations depend on factors within the child, such as hunger, and on others beyond his control, e. g., the amount of milk in the breasts at the time of suckling, and the comfort of the child while nursing.

The apparently arbitrary regime selected by the pediatrist has been chosen because it works. It is in a great measure empirically chosen. It is the mode of feeding that the individual finds works best in the majority of infants that come under his care. It is generally agreed that the regular feeding at stated intervals is desirable. Opinions differ as to amount of food to be given at a feeding and as to the interval that is most desirable. The two are in a measure, reciprocals of each other.

The total daily amount of food necessary for a healthy infant of a given weight and age has been rather satisfactorily determined by the statistical methods of Camerer and the experimental methods of Heubner. One hundred and ten calories of food pro kilo body weight is needed during the first month. This gives the total amount of food for the day. If, now, a three hour interval is selected, eight feedings

8. Ginsberg, H., Tumpowsky, I., and Carlson, A. J.: The Onset of Hunger in Infants After Feeding. A Contribution to the Physiology of the Stomach, Jour. Am. Med. Assn., 1915, lxiv, 1822.

in twenty-four hours, one-eighth of the total amount may be given at a time. If a four hour interval is selected, six feedings of one-sixth the total amount must be given.

The question at once arises, has the infant's stomach capacity enough to receive the large amounts of liquid that are necessitated by the feedings at long intervals? The answer to this question has been sought in two ways. First, the actual capacity of the infant's stomach has been determined post mortem; and second, attempts have been made during life to give these amounts of food. Studies of the actual capacity (after death) of the infant's stomach have been made by the various authors. The picture given by Holt in the fifth edition of his textbook of diseases of children, life-size illustrations, are readily available. They show that the stomach of an infant during the first month has a capacity of 1 to something over 2 ounces. That is, the capacity is not sufficient to receive the amount of breast milk required for each feeding at four hour intervals. Still less would it seem sufficient to receive the greater amount of fluid that is necessary for giving cow's milk in suitable dilution. Clinically, however, the infant's stomach is usually able during life to receive either amount, and that without unpleasant symptoms. The explanation lies in the fact that five, ten, or more minutes is consumed in taking the fluid, and that the liquid begins to leave the stomach within a few minutes after the first enters. The actual volume capacity of the stomach, post mortem or intra vitam, is thus not necessarily a true guide to the amount of fluid to be given at any one time. Nor is it, as a rule, a sufficient guide to the most desirable interval between feedings. It is certain that many infants do unusually well when nursed (or fed) at intervals of four hours from the first days on.

When the stomach has once been filled more or less completely, it seems desirable not to introduce more food until that previously given has completely passed out. Otherwise symptoms of indigestion are likely to result. It may even be that a somewhat longer delay is desirable. A certain period of rest for the gastric glands may be beneficial.

The roentgenogram studies of Pisek and LeWald[9] seem to show that "three hours is practically the emptying time of the child's stomach, and often less than that." Czerny and others had earlier concluded that the stomach of the normal infant empties itself in from about one and a half to two hours. Whether the use of bismuth and other substances for Roentgen-ray work has any influence on the rate of emptying is perhaps debatable; many state that it has not. Normally, the time of emptying the stomach seems to depend on the quan-

9. Pisek and LeWald: The Infant Stomach, Tr. Am. Ped. Soc., 1913, xxv, 150.

tity of food taken, the rate of gastric secretion, and the vigor of gastric (digestion) peristalsis.

In any case satisfactory determination of the capacity of the stomach for receiving an amount of food, and of the time required for emptying the stomach after receiving the amounts given, is not all that is needed for the selection of the optimum amount of food and the optimum interval. It may be well to allow the stomach a period of rest between feedings. It may also be well to await the appearance of the sensation of hunger before introducing more food. Here again there is difficulty.

Until the last few years there has been no certain objective criterion for the existence of hunger. Such a criterion has now been found, it is thought.

In work published by Cannon and Washburn[10] in 1912 and by Carlson[11] in 1913, it seems established that a "subjective sensation of hunger is caused by a certain type of contraction of the fundal end of empty stomach stimulating sensory nerves in the wall of the stomach." These contractions are peculiar to the cardiac and fundal ends of the empty stomach, and are, in normal individuals (adults) at least, "an objective index of hunger." Their presence is determined by introducing into the stomach a small balloon connected with a chloroform manometer. (For technic, see articles here referred to.)

Carlson[8] and his collaborators have applied this method to determine the time of onset of hunger in infants after previous feeding. The determination of this question may aid in fixing the time that should elapse between the nursings of normal infants.

Their observations were made on thirty normal infants, from twenty-four hours to four weeks old. The frequency with which the infants were being fed and the amounts they received are not stated. They seem to have been breast-fed ("nursing") infants. The balloon was introduced into the stomach half an hour or more after feeding and the tracings published were obtained from infants who were asleep or otherwise quiet. Introduction of the balloon directly after nursing led to vomiting of the balloon and part of the food, and restlessness on the part of the child caused the inhibition of the hunger contractions.

Fifty-five observations were made upon the thirty infants. Tracings made from the chloroform manometer while the inflated balloon was in the fundus showed practically no contractions when the stomach was full. As the stomach gradually emptied itself feeble tonus contractions appeared. These increased in rate and intensity until, about two and a half hours after a nursing, they passed over into typical

10. Cannon, W. B., and Washburn, A. L.: Am. Jour. Physiol., 1912, xxix, 441.
11. Carlson, A. J.: Am. Jour. Physiol., 1913, xxxi, 175.

hunger contractions. In Carlson's series the minimum time elapsing before the appearance of hunger contractions was two hours and the maximum time was three hours. The time of onset of hunger contractions after the previous feeding varied for each infant. The hunger contractions of the empty stomach were seen to be modified tonus waves of the fundus of the digesting stomach.

The authors conclude: In the normal individual the presence of vigorous hunger contractions is probably biologic evidence that the stomach is in proper condition to receive fluid. If this is the case, the stomach of a normal infant is ready to receive food from two to three hours after the previous feeding.

From what has already been said, it is clear that, even if the reliability of the method used by Carlson and his associates be granted, many factors must be taken into consideration before pediatrists can accept the above evidence as indicative of the proper feeding interval.[12]

A paper by Smith and LeWald[13] emphasizes the importance of placing infants in a semi-erect position during and immediately after nursing, and puts the instinctive inclination of mothers to lay colicky babies over their shoulders and fondle them, on a scientific basis. In the stomach of every individual there is a certain amount of gas. It may be derived from swallowed air, from gastric fermentation or from the intestines. In the large majority of cases, swallowed air accounts for the gas in the stomach. The size and anatomic relations of the pharynx are such that it is unable to close down completely on the small quantity of fluid swallowed at each gulp and, as a result, a certain amount of the air that is always present in the pharynx is carried down by the contraction of the muscles in the act of swallowing. When food is semisolid and a bolus is formed, less air proportionately is carried down.

Smith and LeWald introduced their study with a consideration of the anatomic position of the stomach. Roentgenography has shown that the stomach is not vertical in position in infants. The stomachs of infants resemble those of adults in a general way. The important features are these:

The esophagus enters the abdomen by an opening in the diaphragm, almost in the midline, in contact with the aorta and the ventral surface of the bodies of the vertebrae. The cardiac orifice lies just to the left of this position and the cardia is firmly held to the posterior abdominal wall by the esophagus as it pierces the diaphragm. The fundus of the stomach lies in the left paravertebral groove, that is, in the lateral recess formed by the projection forward of the vertebral column into the abdominal cavity. The fundus reaches a plane considerably dorsal to the cardiac orifice. It is covered in front only

12. One cannot help wondering how far these waves were not simply evidence of increasing effort on the part of the empty stomach to expel the balloon, an indigestible foreign body.

13. Smith, C. H., and LeWald, L. T.: The Influence of Posture on Digestion in Infancy, Am. Jour. Dis. Child., 1915, ix, 261.

by the liver and extends to the anterior abdominal wall. The pyloric end of the stomach is pushed forward by the vertebral column, pancreas and duodenum. The pyloric opening is directed backward toward the duodenum, but lies in a plane which is ventral to that of the cardia. The cardiac opening is behind the center of the anteroposterior diameter of the stomach.

As food enters the stomach it gravitates to the lowest part, displacing any gas present to the highest part. If the infant is in a horizontal position the liquid food passes to the posterior portion of the stomach, that is, to the fundus, and any gas present is forced to the anterior part of the fundus and toward the right end of the stomach. They say:

> Since the cardiac orifice is situated well back against the vertebral column it follows that it will be covered by the liquid and that the gas cannot escape into the esophagus. It can escape only through the pylorus, if at all. If the amount of food plus gas is enough to distend the stomach, either food or gas must be forced out through the pylorus or regurgitation of food must take place through the esophagus until the tension on the stomach wall is relieved. The horizontal position causes a perfect water-lock to form as far as the gas and the cardiac opening are concerned.
>
> When the child is held upright the liquid gravitates at once to the dependent part of the stomach and displaces the gas to the highest part, that is, to the upper part of the fundus. This makes it possible for the gas to escape by the esophagus, and it often does so at once.

These conditions are well illustrated by roentgenograms. These were obtained from four infants ranging in age from 4 to 7 months, who were given their usual feedings of 4 to 7 ounces of modified milk, to which one-half ounce of bismuth subcarbonate had been added. They showed a progressive accumulation of gas in the stomach during the act of nursing. In two instances this was accompanied by regurgitation or vomiting. In one the accumulation of gas became relatively enormous; the distention of the stomach caused evident distress, and the infant refused to finish the bottle. Changing to an erect position, some minutes afterwards, caused a large eructation of gas, and the child at once stopped crying and went to sleep.

The presence of swallowed air is regarded by Smith and LeWald as objectionable. Extreme distention must be unfavorable to gastric secretion through pressure on the mucosa and blood vessels. The symptoms may often be entirely relieved by assisting the expulsion of the gas by mouth, so that it need not be passed through the intestine. If it does pass through the intestine, it causes colic. A horizontal position in nursing favors the accumulation of gas. Hospital feeding cases are often examples of the bad result of this. Except in the case of feeble infants, the feeding should be taken in five to ten minutes, or at most in fifteen. There are fewer disadvantages in having several holes in the nipple so that the milk runs freely, than in prolonging the nursing.

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